Glycemic Control in Diabetic Pregnancies:

Effects on Fetal and Maternal Outcome

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Academic dissertation

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To my family

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I Suhonen L, Teramo K. Hypertension and pre-eclampsia in women with gestational glucose intolerance. Acta Obstet Gynecol Scand 1993;72:269-72

II Suhonen L, Hiilesmaa V, Kaaja R, Teramo K. Detection of pregnancies with high risk of fetal macrosomia among women with gestational diabetes mellitus. Acta Obstet Gynecol Scand 2008;87:940-5

III Suhonen L, Hiilesmaa V, Teramo K. Glycaemic control during early pregnancy and fetal malformations in women with Type I diabetes mellitus. Diabetologia 2000;43:79-82

IV Hiilesmaa V, Suhonen L, Teramo K. Glycaemic control is associated with pre-eclampsia but not with pregnancy induced hypertension in women with Type I diabetes mellitus. Diabetologia 2000;43:1534-9

ABBREVIATIONS

ANOVA	Analysis of variance
BMI	Body mass index
CI	Confidence interval
CNS	Central nervous system
CV	Coefficient of variation
EPO	Erythropoietin
FGF	Fibroblast growth factor
GDM	Gestational diabetes mellitus
HbA_{1c}	Hemoglobin A_{1c}
HbF	Fetal hemoglobin
HPLC	High performance liquid chromatography
IGF	Insulin-like growth factor
IU	International unit
IUGR	Intrauterine growth restriction
LGA	Large-for-gestational age
MRI	Magnetic resonance imaging
OGTT	Oral glucose tolerance test
OR	Odds ratio
PDA	Patent ductus arteriosus
PE	Preeclampsia
PIH	Pregnancy-induced hypertension
RDS	Respiratory distress syndrome
RR	Relative risk
SD	Standard deviation
STAKES	National Research and Development Centre for Welfare and Health
VSD	Ventricular septal defect
WHO	The World Health Organization

ABSTRACT

Background: Both maternal and fetal complications are increased in diabetic pregnancies. Although hypertensive complications are increased in pregnant women with pregestational diabetes, reports on hypertensive complications in women with gestational diabetes mellitus (GDM) have been contradictory. Congenital malformations and macrosomia are the main fetal complications in Type 1 diabetic pregnancies, whereas fetal macrosomia and birth trauma but not congenital malformations are increased in GDM pregnancies.

Aims: To study the frequency of hypertensive disorders in gestational diabetes mellitus. To evaluate the risk of macrosomia and brachial plexus injury (Erb's palsy) and the ability of the 2-hour glucose tolerance test (OGTT) combined with the 24-hour glucose profile to distinguish between low and high risks of fetal macrosomia among women with GDM.
To evaluate the relationship between glycemic control and the risk of fetal malformations in pregnancies complicated by Type 1 diabetes mellitus. To assess the effect of glycemic control on the occurrence of preeclampsia and pregnancy-induced hypertension in Type 1 diabetic pregnancies.

Subjects: A total of 986 women with GDM and 203 women with borderline glucose intolerance (one abnormal value in the OGTT) with a singleton pregancy, 488 pregnant women with Type 1 diabetes (691 pregnancies and 709 offspring), and 1154 pregnant non-diabetic women (1181 pregnancies and 1187 offspring) were investigated.

Results: In a prospective study on 81 GDM patients the combined frequency of preeclampsia and PIH was higher than in 327 non-diabetic controls (19.8% vs 6.1%, $p<0.001$). On the other hand, in 203 women with only one abnormal value in the OGTT, the rate of hypertensive complications did not differ from that of the controls. Both GDM women and those with only one abnormal value in the OGTT had higher pre-pregnancy weights and BMIs than the controls.

In a retrospective study involving 385 insulin-treated and 520 diet-treated GDM patients, and 805 non-diabetic control pregnant women, fetal macrosomia occurred more often in the insulin-treated GDM pregnancies (18.2%, $p<0.001$) than in the diet-treated GDM pregnancies (4.4%), or the control pregnancies (2.2%). The rate of Erb's palsy in vaginally delivered infants was 2.7% in the insulin-treated group of women and 2.4% in the diet-treated women compared with 0.3% in the controls ($p<0.001$). The cesarean section rate was more than twice as high (42.3% vs 18.6%) in the insulin-treated GDM patients as in the controls.

A major fetal malformation was observed in 30 (4.2%) of the 709 newborn infants in Type 1 diabetic pregnancies and in 10 (1.4%) of the 735 controls (RR 3.1, 95% CI 1.6–6.2). Even women whose levels of HbA_{1c} (normal values less than 5.6%) were only slightly increased in early pregnancy (between 5.6 and 6.8%) had a relative risk of fetal malformation of 3.0 (95% CI 1.2–7.5). Only diabetic patients with a normal HbA_{1c} level (<5.6%) in early pregnancy had the same low risk of fetal malformations as the controls.

Preeclampsia was diagnosed in 12.8% and PIH in 11.4% of the 616 Type 1 diabetic women without diabetic nephropathy. The corresponding frequencies among the 854 control women were 2.7% (OR 5.2; 95% CI 3.3–8.4) for preeclampsia and 5.6% (OR 2.2, 95% CI 1.5–3.1) for PIH. Multiple logistic regression analysis indicated that glycemic control, nulliparity, diabetic retinopathy and duration of diabetes were statistically significant independent predictors of preeclampsia. The adjusted odds ratios for preeclampsia were 1.6 (95% CI 1.3–2.0) for each 1%-unit increment in the HbA_{1c} value during the first trimester and 0.6 (95% CI 0.5–0.8) for each 1%-unit decrement during the first half of pregnancy. In contrast, changes in glycemic control during the second half of pregnancy did not alter the risk of preeclampsia.

Conclusions: In type 1 diabetic pregnancies it is extremely important to achieve optimal glycemic control before pregnancy and maintain it throughout pregnancy in order to decrease the complication rates both in the mother and in her offspring. The rate of fetal macrosomia and birth trauma in GDM pregnancies, especially in

the group of insulin-treated women, is still relatively high. New strategies for screening, diagnosing, and treatment of GDM must be developed in order to decrease fetal and neonatal complications.

INTRODUCTION

Diabetes mellitus complicates 3–5% of pregnancies increasing the risk of both maternal and perinatal morbidity and mortality (Gabbe and Graves 2003).

Gestational diabetes mellitus (GDM) is defined as glucose intolerance of variable severity with onset or first recognition during pregnancy (Metzger and Coustan 1998). It complicates 2–5% of all pregnancies (Gabbe and Graves 2003). Obesity is an increasing problem worldwide (Catalano 2007a) and overweight women are especially at risk of developing GDM (Callaway et al. 2006, Chu et al. 2007). Fetal macrosomia is the most important perinatal complication in women with GDM (Gabbe and Graves 2003). The incidence of trauma among mothers and their offspring is increased in cases of vaginal delivery after pregnancies complicated by GDM (Langer et al. 2005b). The incidence of cesarean section delivery is also increased in GDM pregnancies (Sermer et al. 1998). Gestational diabetes mellitus may precede Type 2 diabetes mellitus later in life (Ben-Haroush et al. 2004).

Type 2 diabetes mellitus, which is characterized by insulin resistance and relative insulin deficiency (Maedler 2008), occurs later in life and is often associated with obesity.The incidence of Type 2 diabetes mellitus has increased during the last two decades worldwide. This is also reflected in an increase in Type 2 diabetic pregnancies (Feig and Palda 2002, Dunne 2005). The incidence of obstetric and perinatal complications in Type 2 diabetic pregnancies equals or is even higher than that associated with Type 1 diabetic pregnancies (Macintosh et al. 2006, Bell et al. 2008).

Type 1 diabetes mellitus is an autoimmune condition, in which the beta cells of the pancreas are destroyed eventually necessitating insulin replacement therapy (Taplin and Barker 2008). It generally occurs early in life and complicates 0.2–0.4% of pregnancies (Engelgau et al. 1995, von Kries et al. 1997). In Finland the incidence of Type 1 diabetes is the highest in the world and in Finnish children it is increasing even faster than before (Tuomilehto et al. 1999, Harjutsalo et al.

2008). It has been estimated that 0.6% of childbirths are complicated by Type 1 diabetes in Finland.

Major fetal malformations are often associated with poor glycemic control before or during early pregnancy (Mills et al. 1979, Kitzmiller et al. 1996). Fetal malformations represent one of the main causes of increased perinatal mortality among pregnant women with pregestational diabetes (Gabbe and Graves 2003). The prevalence of major congenital malformations in Type 1 and Type 2 diabetic pregnancies is 2–4 times higher than in the general population (Macintosh et al. 2006, Yang et al. 2006).

Fetal macrosomia is one of the main perinatal complications in all types of diabetic pregnancy, especially in women with poor glycemic control (Gabbe and Graves 2003). It has been suggested that all infants of women with Type 1 diabetes are actually macrosomic (Bradley et al. 1988). Fetal macrosomia increases the risk of birth trauma, particular brachial plexus nerve injury (Erb's palsy) (Christoffersson and Rydhstroem 2002). Fetal hypoxia (Teramo et al. 2004) and neonatal asphyxia (Barnes-Powell 2007) are also increased in Type 1 diabetic pregnancies. The risk of preeclampsia is increased in women with Type 1 diabetes (Sibai 2000), especially those with diabetic nephropathy (Howarth et al. 2007). Diabetic nephropathy also increases the risk of fetal growth restriction (Reece et al. 1998).

In the present studies the effect of glycemic control on the occurrence of preeclampsia and pregnancy-induced hypertension (PIH) in GDM or Type 1 diabetic pregnancies was assessed. The relationship between glycemic control and the risk of fetal malformations in pregnancies complicated by Type 1 diabetes mellitus was also evaluated. Finally, a method was developed for detecting women with GDM at a high risk of delivering a macrosomic infant.

REVIEW OF THE LITERATURE

1. Glucose metabolism and pregnancy

1.1 Normal pregnancy

Maternal glucose metabolism changes throughout pregnancy. Concentrations of fasting blood glucose decreases as early as in the first trimester and remain low throughout pregnancy compared with fasting levels before pregnancy (Pedersen 1977a, Mills et al. 1998). In contrast, postprandial glucose values increase from the 16th pregnancy week until the 36th pregnancy week (Siegmund et al. 2008). During the first half of pregnancy, basal insulin levels are normal or slightly elevated, coinciding with a decrease of about 10% in fasting blood glucose values (Kühl 1975, Freinkel 1985, Hollingsworth 1985). Basal insulin levels increase by 50–80% in the third trimester (Kühl 1975). Normally the development of increasing insulin resistance during pregnancy is compensated for by a simultaneous increase in insulin secretion (Ryan et al. 1985, Buchanan et al. 1990, Sivan et al. 1997). Mild glucosuria in normoglycemic mothers is considered physiological, because glucose reabsorption from the renal tubules is decreased during pregnancy (Davison and Dunlop 1980).

Placental glucose transfer from mother to fetus takes place by facilitated diffusion (Leonce et al. 2006). The transport mechanism is controlled by blood glucose concentrations both in the fetus and in the mother. The primary transporter responsible for maternal-to-fetal glucose transport, placental glucose transporter 1 (GLUT1), was first described by Fukumoto et al. (1988) and Bell et al. (1990). Insulin-like growth factors IGF-1 and IGF-2 also stimulate glucose transport across the placenta (Kniss et al. 1994).

Fetal blood glucose levels are lower than maternal levels, but they correlate linearly (Raivio and Teramo 1968, Hay and Sparks 1985). Fetal insulin

production starts during the first trimester (Adesanya et al. 1966), but it responds to increased glucose levels only during the latter half of pregnancy (Adam et al. 1969). Free insulin does not cross the placenta (Adam et al. 1969).

1.2 Gestational diabetes mellitus

Impaired insulin secretion may vary from complete failure (such as in Type 1 diabetes) to a partial defect occurring only under circumstances of increased need such as pregnancy (GDM) or obesity (Type 2 diabetes). The basic metabolic defect in women with GDM is the limited capacity of pancreatic beta cells to increase their insulin secretion to compensate for the progressively increasing insulin resistance during pregnancy (Buchanan et al. 1990, Catalano et al. 1993, Xiang et al. 1999). Postprandial hyperglycemia is common in women with GDM (Buchanan et al. 1990). Because postprandial glucose levels are dependent on the carbohydrate and fat content of the meal, the main treatment in GDM pregnancies is dietary intervention.

Gestational diabetes mellitus is defined as any degree of glucose intolerance with the onset or first recognition during pregnancy. The diagnosis is based on an oral glucose tolerance test (OGTT) done with a 75 g glucose load. Diagnostic criteria for the 75-g OGTT are for fasting plasma glucose 5.3, for the 1-hour value 10.0 and for the 2-hour value 8.6 mmol/l (Metzger and Coustan 1998, The Finnish Working Group on Gestational Diabetes 2008). Until 2008 the following criteria were used in Finland to diagnose GDM according to the 2-hour OGTT: two or more glucose values above: fasting 5.1, 1-hour 10.00 and 2-hour 8.7 mmol/l (venous plasma or capillary whole blood). The cut-off values were for venous whole blood 4.5, 9.1 and 7.9 mmol/ for fasting, 1-hour and 2-hour, respectively (Teramo 2006).

The prevalence of GDM differs considerably in different ethnic populations. In the United States the prevalence of GDM ranges from 1 to 14%, with 2–5% being the most common rate (Ben-Haroush et al. 2008). The adjusted relative risk of

GDM in black women has been reported to be 1.81 (95% CI 1.13–2.89) and in Hispanic women 2.45 (95% CI 1.48–4.04) compared with Caucasian women (Dooley et al. 1991). In another study, in Australia Asian women were more likely to have GDM than Caucasian women (Gunton et al. 2001).

Obesity among pregnant women is increasing worldwide (Catalano 2007a). This is also true in Finnish women with GDM, Type 1 or Type 2 diabetes (Teramo, unpublished observations). Elevated BMI is clearly associated with an increased risk of GDM (Bottalico 2007). Chu et al. (2007) reported, in a meta-analysis including twenty studies, that unadjusted ORs of GDM were 2.14 (95% CI 1.82–2.53), 3.56 (95% CI 3.05–4.21), and 8.56 (95% CI 5.07–16.04) among overweight (BMI 25–29.9 kg/m^2), obese (30–40 kg/m^2) and severely obese (>40 kg/m^2) pregnant women compared with normal-weight (BMI <25.0 kg/m^2) pregnant women, respectively. Callaway et al. (2006) showed that overweight (BMI 25.01–30 kg/m^2), obese (30.01–40 kg/m^2) and morbidly obese women (>40 kg/m^2) were at increased risk of GDM, with ORs of 1.78 (95% CI 1.25–2.52), 2.95 (95% CI 2.05–4.25) and 7.44 (95% CI 4.42–12.54), respectively. Also, excessive weight gain during pregnancy can lead to an increased risk of GDM (Kabiru and Raynor 2004). Furthermore, Villamor and Cnattingius (2006) showed that when pre-pregnancy BMI increased from the first to the second pregnancy, the occurrence of GDM also increased in the subsequent pregnancy. Women who gained 3 or more units of BMI by their next pregnancy had an adjusted OR for GDM of 2.09 (95% CI 1.68–2.61). The association between the risk of GDM and weight gain was linear, and was also noted in women with normal pre-pregnancy BMI, which suggests that even a modest increase in BMI could result in perinatal complications. In a Swedish study, Zetterström et al. (2005) found that chronic hypertensive disease is also an independent risk factor of GDM (OR 1.8, 95% CI 1.4–2.4).

The main goal of treatment in GDM pregnancies is to achieve normoglycemia, i.e. to prevent both fasting and postprandial hyperglycemia from the diagnosis of GDM until labor and delivery. When women with GDM achieve normoglycemia, their weight gain during pregnancy is usually less than that of healthy pregnant

women (Suhonen and Teramo 1993). If normoglycemia cannot be maintained by diet alone, insulin therapy is started. Recently, it has been reported that treatment with glyburide alone (Langer et al. 2000, 2005a) or with metformin alone or with supplemental insulin (Rowan et al. 2008) is an effective and safe treatment option for women with GDM. Immediately after delivery, women with GDM rarely need to continue with insulin or oral medication treatment in order to maintain euglycemia. However, they remain at an increased risk of Type 2 diabetes mellitus later in life and they should therefore have regular check-ups for blood glucose levels for the rest of their lives.

1.3 Type 1 diabetes mellitus

In Type 1 diabetes mellitus, insulin secretion is either totally lacking or severely impaired. During pregnancy in Type 1 diabetics, the requirement of insulin to maintain the same glycemic level increases from the end of the first trimester until the end of pregnancy. On average, the insulin need increases from 0.7 IU/kg body weight per day in the first trimester to 0.8 IU/kg per day in the second trimester and to 0.9 IU/kg per day in the third trimester until 36 weeks of pregnancy. At term the insulin requirement is 1.0 IU/kg per day (Jovanovic and Kitzmiller 2008). However, individual variation in the increase of insulin requirement during pregnancy is relatively large. During the first weeks of pregnancy, insulin sensitivity is often increased, which at least partly explains the increase in hypoglycemic episodes in Type 1 diabetic mothers during the first trimester (Nielsen et al. 2008). Gabbe and Graves (2003) reported that insulin requirements increase throughout pregnancy, most markedly in the period between 28 and 32 weeks of gestation, after which it can actually decrease in some Type 1 diabetic mothers. After parturition, the daily insulin requirement decreases within a day or two to the pre-pregnancy level (Buchanan et al. 1985, Jovanovic and Kitzmiller 2008) and when lactation starts, even to a lower level.

1.4 Monitoring glycemic control

Optimal glycemic control during diabetic pregnancy is the basis for good outcome, both for the mother and her newborn infant (Pedersen 1977d, Langer et al. 1989, Inkster et al. 2006). Monitoring of both preprandial and postprandial blood glucose values is important in order to achieve euglycemia (Crowther et al. 2005, Fadl et al. 2006, Jovanovic 2008, Kitzmiller et al. 2008). Recently, subcutaneous continuous glucose monitoring has increasingly been used to achieve maternal normoglycemia in order to reduce the risk of fetal macrosomia and neonatal hypoglycemia in diabetic pregnancies (Kerssen et al. 2007, Kestilä et al. 2007, Stenninger et al. 2008).

Monitoring glycemic control has been greatly improved by the introduction of methods which reflect the mean blood glucose level over a prolonged period of time. The chemical reaction between glucose and proteins results in production of nonenzymatically glycated proteins in blood and tissues. The level of glycation of hemoglobins is proportional to the average glucose concentration during the previous 4 to 8 weeks (Bunn et al. 1978) and therefore it does not detect rapid changes in plasma glucose concentration. The glycation level also depends on the lifespan of red blood cells in the circulation. The turnover rate of red blood cells during pregnancy is about 90 days, compared with 120 days in non-pregnant adults (Albertson and Jovanovic 2008). The amount of glycated hemoglobin is expressed as a percentage of the total hemoglobin.

Early methods for fractionation of hemoglobin included cation exchange column chromatography. The procedures were elaborate and time-consuming, requiring several days of work. Subsequently, automated methods, such as high-performance liquid chromatography (HPLC), were developed (Dunn et al. 1979, Gruber and Koets 1979). Stenman et al. (1984) developed a fully automated rapid HPLC method for the measurement of hemoglobin A_{1c} (HbA_{1c}) levels. The method permits separation and quantification of HbA_{1c}, even in the presence of elevated levels of fetal hemoglobin (HbF). It has been shown recently that a 1% unit increase in the HbA_{1c} level equals a mean plasma glucose increase of 1.6 mmol/l in non-pregnant diabetic adults (Nathan et al. 2008).

Several recommendations exist for evaluating glycemic control in women with GDM**.** A relatively recent recommendation is that both pre- and postprandial glucose levels should be measured four times a day (Gabbe and Graves 2003). The optimal time for measuring the postprandial glucose level is one hour after the meal (Bühling et al. 2005). Insulin- treated women with GDM should measure their blood glucose level 5-6 times each day (Jovanovic 2008). Subcutaneous continuous glucose monitoring is a new method for measuring glucose values continuously over several days. However, its advantage over self-monitoring of blood glucose still needs to be demonstrated (Yogev et al. 2008, Kestilä et al. 2007).

2. Maternal outcome

2.1 Maternal hypoglycemia

Maternal hypoglycemia is a well-recognized and potentially dangerous complication of intensive insulin therapy in pregnant women with Type 1 diabetes. Severe hypoglycemia is defined as impairment of consciousness of a diabetic, who needs help from another person to administer glucose orally or to give a glucagon injection or intravenous glucose infusion (ADA workgroup 2005). Severe hypoglycemia during pregnancy occurs in 41–45% of Type 1 diabetic women (Evers et al. 2002a, Nielsen et al. 2008) The risk of severe hypoglycemia is greatest during the first trimester of pregnancy (Rosenn et al. 1995, Evers et al. 2002a, Nielsen et al. 2008). Subjective symptoms of low blood glucose levels are often diminished during pregnancy, which decreases the patient's awareness of hypoglycemia (Björklund et al. 1998, Nielsen et al. 2008). Furthermore, pregnancy attenuates glucose counter-regulation mechanisms during hypoglycemia in Type 1 diabetic women (Diamond et al. 1992, Rosenn et al. 1996). Therefore, intensive insulin therapy during pregnancy predisposes patients to severe hypoglycemia in cases of Type 1 diabetes. Recurrent severe maternal

hypoglycemic episodes during pregnancy can result in impairment of cognitive functions of the mother (Langan et al. 1991, Deary and Frier 1996).

Animal studies indicate that maternal hypoglycemia is teratogenic during organogenesis (Buchanan et al. 1986, Smoak and Sadler 1990, ter Braak et al. 2002). However, studies in pregnant women with Type 1 diabetes have not revealed any association between maternal hypoglycemia and adverse fetal outcome (Rosenn and Miodovnik 2000) or diabetic embryopathy (Mills et al. 1988, Steel et al. 1990, Kitzmiller et al. 1991, ter Braak et al. 2002). Similarly, no abnormal changes in fetal behavior have been reported in women with Type 1 diabetes during induced moderate maternal hypoglycemia (Diamond et al. 1992, Rosenn et al. 1996).

2.2 Preeclampsia and pregnancy-induced hypertension

Preeclampsia is defined as hypertension with a diastolic blood pressure repeatedly above 90 mmHg during the second half of pregnancy, in combination with proteinuria (Cunningham and Lindheimer 1992, Roberts and Redman 1993). However, the definition of preeclampsia varies in different publications (Harlow and Brown 2001). Pregnancy-induced hypertension (PIH) is defined as high blood pressure (diastolic blood pressure repeatedly over 90 mmHg) during the second half of pregnancy without proteinuria.

Preeclampsia is a disease of unknown etiology (Redman and Sargent 2005). However, it is characterized by widespread endothelial cell dysfunction (Roberts et al. 1989, 1991, Rodie et al. 2004, Sibai et al. 2005). Moreover, preeclampsia is also characterized by insulin resistance, immune maladaption, coagulation defects and increased systemic inflammatory response (Kaaja et al. 1999, Rodie et al. 2004, Kaaja and Greer 2005, Sibai et al. 2005).

Preeclampsia complicates about 4% of pregnancies in nulliparous women and about 2% in multiparous women (Sibai et al. 2005), and it is one of the major pregnancy complications causing increased morbidity and mortality in both the mother and the newborn infant (Roberts and Cooper 2001). Preeclampsia and PIH increase the risk of iatrogenic preterm birth and intrauterine growth restriction and these women are at an increased risk to obtain cardiovascular disease later in life (Rodie et al. 2004, Sibai et al. 2005). In a Swedish study 5.2% of 10 666 pregnant women developed preeclampsia, and 4.4% developed PIH (Ros et al. 1998). In another Swedish study, Östlund et al. (2004) analyzed 430 852 singleton deliveries using the Swedish Medical Birth Registry and found that the incidence of preeclampsia was 2.8% in non-diabetic women. Eclampsia (maternal seizures) is a rare complication of pregnancy in the developed world. In Finland, the incidence of eclampsia was 2.4 per 10 000 births in the 1990s (Ekholm et al. 1999). Similarly, in a Swedish study the incidence of eclampsia was 3.3 (Kullberg et al. 2002) and in a study in the UK, 2.7 per 10 000 births (Knight 2007).

Nulliparity is associated with a 2.4- to 2.6-fold elevated risk of preeclampsia (Funai et al. 2005, Luo et al. 2007). Advanced maternal age and multiple pregnancies also increase the risk (Coonrod et al. 1995, Funai et al. 2005). Women with previous severe preeclampsia have a high risk of preeclampsia in subsequent pregnancies (Sibai et al. 1986, 1991). A family history of preeclampsia is associated with a three- to four-fold increased risk of preeclampsia (Cincotta and Brennecke 1998).

2.2.1 Impact of obesity

Obesity may be the most common cause of insulin resistance. Insulin secretion is three to four times higher in obese subjects than in lean controls (Polonsky et al. 1996). Obesity is a risk factor as regards developing preeclampsia as well as PIH (Sibai et al. 1995, Jensen et al. 2003a). Ros et al. (1998) compared underweight women (BMI <19.8 kg/m^2) with obese women (BMI >29 kg/m^2). The obese women had increased risks of both preeclampsia (OR 5.19, 95% CI 2.35–11.48)

and PIH (OR 4.85, 95% CI 1.97–11.92). Even in normal pregnancy, insulin resistance increases, but this change is exaggerated in women with preeclampsia (Rodie et al. 2004). In a recent study, the risks of preeclampsia and PIH were 1.9- and 1.5-fold higher, respectively, in overweight women (prepregnancy BMI 26.1–29 kg/m^2) than in normal weight women (BMI 19.8–26 kg/m^2) (Belogolovkin et al. 2007).

Weight gain during pregnancy has gradually increased in the United States during the last 15–20 years (Catalano 2007b). Excessive maternal weight gain during pregnancy increases the rates of adverse obstetric and neonatal outcomes. DeVader et al. (2007) reported that in pregnancies with a weight gain over 15.9 kg, preeclampsia occurred more frequently (OR 1.88, 95% CI 1.74–2.04) than in pregnancies with a recommended weight gain of 11.4–15.9 kg. On the other hand, preeclampsia occurred more seldom (OR 0.56, 95% 0.49–0.64) when the weight gain was under 11.4 kg. Similarly, Kiel et al. (2007), using the same birth registry, reported that the risk of preeclampsia was significantly lower when the weight gain in overweight and obese women was less than 6.8 kg. In the study by Villamor and Cnattingius (2006) an increase in pre-pregnancy BMI of at least 3 units from the first to the second pregnancy was associated with increased frequencies of both preeclampsia (OR 1.78, 95% CI 1.52–9.08) and PIH (1.76, 95% CI 1.18–2.61). In another Swedish study Zetterström et al. (2005) reported that chronic hypertensive disease is an independent risk factor of preeclampsia (OR 3.8, 95% CI 3.4–4.3).

2.2.2 Gestational diabetes mellitus

Reports on the relationship between GDM and preeclampsia have been contradictory. Jacobson and Cousins (1989) and Schaffir et al. (1995) found no relationship between GDM and pregnancy-induced hypertensive disorders. However, Nordlander et al. (1989) and Hunger-Dathe et al. (2005) reported that women with GDM more frequently had preeclampsia than healthy controls. The incidence of preeclampsia in women with GDM has been reported to range from

6.1% to 14.4% (Starcevic and Djelmis 2004, Yogev et al. 2004b, Östlund et al. 2004 , Hunger-Dathe et al. 2005). Even minor degrees of glucose intolerance are associated with an increased incidence of preeclampsia (Sermer et al. 1995, Khan and Daya 1996). Lindsay et al. (1989) found that the incidence of preeclampsia was 7.9% in women with one abnormal value in the OGTT, compared with 3.3% in healthy controls. Ros et al. (1998) showed that GDM was significantly associated with an increased risk of preeclampsia (OR 3.11, 95% CI 1.61–6.00). In the study of Östlund et al. (2004) the adjusted OR for GDM as a risk factor of preeclampsia was 1.61 (95% CI 1.39–1.86).

Barden et al. (2004) reported that insulin resistance in women with GDM precedes the development of preeclampsia. Yogev et al. (2004a) found that GDM women who developed preeclampsia had significantly higher systolic and diastolic blood pressure values throughout the first and second trimester of pregnancy compared with GDM women without preeclampsia. In another study, Yogev et al. (2004b) reported that the rate of preeclampsia was influenced by the severity of GDM, and improved glycemic control during pregnancy decreased the rate of preeclampsia. Similarly, in the study of Starcevic and Djelmis (2004) preeclampsia frequency increased with increasing blood glucose values. However, when glucose values decreased during pregnancy, the frequency of preeclampsia decreased.

2.2.3 Type 1 diabetes mellitus

It has long been known that Type 1 diabetes mellitus considerably increases the risk of preeclampsia (White 1949, Kyle 1963, Pedersen et al. 1974, Reece 1998). In the study of Ros et al. (1998) Type 1 diabetes was associated with an increased risk of preeclampsia (OR 5.58, 95% CI 2.72–11.43. Furthermore, Type 1 diabetic women with vascular complications are more likely to develop preeclampsia (OR 3.5, 95% CI 1.28–9.53) than women without vascular complications (Howarth et al. 2007). Sibai et al. (2000) reported an overall incidence of preeclampsia of 20% in Type 1 diabetic women. The frequency of preeclampsia rose significantly

with increasing severity of diabetes according to White's classification (in classes R-F it was 36%). The risk of preeclampsia is over 50% in women with diabetic nephropathy (White 1949, Kitzmiller et al. 1981, Ekbom et al. 2001). Even microalbuminuria in early pregnancy in women with Type 1 diabetes increases the risk of preeclampsia more than in uncomplicated Type 1 diabetic pregnancies (Combs et al. 1993, Ekbom et al. 2000, 2001).

Gordin et al. (2007) showed that preeclampsia but not PIH in women with type 1 diabetes may be a risk factor for diabetic nephropathy later in life. However,it has also been reported that Type 1 diabetes mellitus is associated with an increased incidence of PIH (Garner et al. 1990, Siddiqi et al. 1991).

The results of several studies suggest an association between poor glycemic control in early pregnancy in women with Type 1 diabetes, and preeclampsia (Combs et al. 1993, Rosenn et al. 1993, Hsu et al. 1996, 1998, Hanson and Persson 1998). Hsu et al. (1996) reported that an improvement of glucose control during pregnancy reduced the risk of preeclampsia. Similarly, Temple et al. (2006) reported that HbA_{1c} levels were higher at 24 weeks of pregnancy in Type 1 diabetic women with preeclampsia than in women without preeclampsia.

2.3 Cesarean section

Women with GDM (Sermer et al. 1998, Langer et al. 2005b) and Type 1 diabetes (El-Sayed and Lyell 2001) have an increased risk of cesarean section delivery. The majority of diabetic women with vascular complications are delivered by cesarean section.

Fetuses of diabetic women are frequently macrosomic (Bradley et al. 1988, Schwartz and Teramo 2000), which increases the rate of cesarean section deliveries. In a study by Jolly et al. (2003), macrosomia, defined as birth-weight

over the 90th percentile, was more likely in women with pregestational diabetes (OR 6.97, 95% CI 5.36–8.16) and GDM (OR 2.77, 95% CI 2.51–3.07) and this increased the risk of emergency cesarean sections (OR 1.84, 95% CI 1.75–1.93). Steer (2004) reported that women with GDM and overt diabetes had a greater likelihood of delivering an infant weighing over 4000 g than women with normal glucose tolerance and that macrosomic fetuses were more than twice as likely to be delivered by emergency cesarean section as fetuses weighing less than 4000 g. The increased risk of maternal complications in diabetic women seems at least partly to be related to emergency cesarean section deliveries (Nasrallah et al. 2004).

Although fetal macrosomia is the leading reason for cesarean delivery in diabetic women, chronic fetal hypoxia, particularly in women with poor glycemic control during the last weeks of pregnancy, also increases the risk of cesarean delivery (Teramo et al. 2004).

2.4 Maternal childbirth trauma

Delivery of a macrosomic infant increases the risk of both maternal and neonatal injury. In a study by Stotland et al. (2004), diabetes was associated with macrosomia, fourth-degree perineal lacerations and postpartum hemorrhage. Both forceps and vacuum extraction deliveries are additional risk factors for trauma. In a study by Johnson et al. (2004) forceps delivery was associated with an increase in major perineal and vaginal tears (OR 1.85, 95% CI 1.27–2.69). Jolly et al. (2003) analyzed data from 350 311 singleton pregnancies between 1988 and 1997 using logistic regression analysis and found that macrosomia, defined as birth-weight over 4000 g, predicted increased risks of both third degree perineal lacerations (OR 2.73; 95% CI 2.30–3.23) and postpartum hemorrhage (OR 2.10; 95% CI 1.93–2.10).

2.5. Maternal mortality

Maternal mortality is defined by the World Health Organization (WHO) as pregnancy-related (accidents excluded) death rate per 100 000 during pregnancy or within 42 days after delivery. In a review including the English literature from 1975 to 2001 and covering publications evaluating maternal mortality in relation to the mode of delivery, Vadnais and Sachs (2006) reported that the overall maternal mortality rate ranged from 6 to 54 deaths per 100 000 live births. Operative delivery clearly is associated with an increased risk of maternal mortality. Cesarean section for any reason is associated with a 3–13 times increased risk compared with vaginal delivery. In a study carried out in the Netherlands and covering 1983 to 1992, the risk of dying in connection with cesarean delivery was 13 per 100 000 operations (Schuitemaker et al. 1997), which was 3 times the risk of maternal mortality after vaginal delivery.

The incidence of maternal mortality in women with Type 1 diabetes is about 0.5% (Gabbe et al. 1976, Cousins 1987). Leinonen et al. (2001) reported the same maternal mortality rate (0.51%, or 5/972) among consecutive Type 1 diabetic mothers with childbirth at the University Central Hospital of Helsinki between 1975 and 1997. It was 109 times greater than that in the general population, but only 3.4 times greater than that in non-pregnant women with Type 1 diabetes of the same age in Finland (Lounamaa 1993). Severe hypoglycemia, massive bleeding, anesthetic complications and high maternal age are important contributing factors to maternal deaths in Type 1 diabetic pregnancies (Schuitemaker et al. 1997, Leinonen et al. 2001).

3. Fetal outcome

3.1 Malformations

The incidence of congenital malformations is two to six times higher in pregnancies of women with Type 1 diabetes mellitus than in healthy women (Garner 1995, Kitzmiller et al. 1996, Platt et al. 2002, Vääräsmäki et al. 2002, Macintosh et al. 2006, Yang et al. 2006). The most common congenital malformations among women with Type 1 diabetes are cardiac, skeletal, CNS, uro-genital, gastro-intestinal, and facial malformations (Merlob 2008).

The majority of the studies have demonstrated a relationship between maternal hyperglycemia in early pregnancy and the occurrence of malformations (Miller et al. 1981, Ylinen et al. 1984, Rose et al. 1988, Greene et al. 1989, Nielsen et al. 2006). Preconception counseling, pregnancy planning and improvement of glycemic control before conception are associated with a decrease in the rate of malformations (Fuhrmann et al. 1983, Mills et al. 1988, Steel et al. 1990, Kitzmiller et al. 1991, McElvy et al. 2000, Evers et al. 2004, Inkster et al. 2006, Pearson et al. 2007). Most fetal malformations start to develop already before the 7^{th} week of pregnancy (Mills et al. 1979). Therefore, it is of utmost importance to achieve and maintain euglycemia already before pregnancy.

Although a strong association exists between hyperglycemia and malformations, the exact mechanism or mechanisms responsible for abnormal fetal development have not been completely elucidated. Experimental studies suggest that oxidative stress may have an important role in the teratogenicity of diabetic pregnancies (Cederberg and Eriksson 2005). Eriksson and coworkers have shown that folic acid supplementation alone or in combination with vitamin E decreases the rate of malformation in the embryos of diabetic rats (Wentzel et al. 2005, Gäreskog et al. 2006).

The prevalence of congenital malformations among the offspring of mothers with gestational diabetes mellitus is similar to or only slightly higher than that in the general non-diabetic obstetric population (Janssen et al. 1996, Aberg et al. 2001). It has been suggested that a subgroup with an increased risk of malformations exists among women with GDM, perhaps as a result of pregestational but undetected Type 2 diabetes (Martínez-Frías et al. 1998, Aberg et al. 2001).

3.2 Fetal growth

3.2.1 Normal growth

Fetal growth is primarily controlled by the capability of the placenta to transport nutrients and oxygen to the fetus (Carrera and Devesa 1998). Normal fetal growth is proportional and linear (Elejalde and de Elejalde 1986). Catecholamines, angiotensin II, aldosterone and prostaglandins play important roles in maintaining uteroplacental blood flow and are indirectly involved in fetal growth by ensuring adequate concentrations of oxygen**,** glucose and nutrients to the fetus (Carrera et al. 1998). Human chorionic somatomammotropin is an important placental hormone related to fetal growth (Carrera et al. 1998, Jovanovic and Kitzmiller 2008). Only 10% of the fetal weight at term is reached during the first half of pregnancy and 2/3 is acquired during the last trimester. Fetal weight gain occurs mainly in the third trimester when fetal insulin acts as a strong growth-promoting hormone (Hill 1976). Locally produced peptide growth factors coordinate fetal growth (Hill et al. 1998). The insulin-like growth factors IGF-1 and IGF-2 in particular play an important regulatory roles in fetal growth (Forbes and Westwood 2008). In addition, fibroblast growth factor-2 (FGF-2) has been shown to be involved in the regulation of fetal growth (Hill et al. 1998). Maternal and fetal serum levels of FGF-2 both correlate directly with fetal and placental size (Hill et al. 1995).

Maternal pre-pregnancy weight has a strong association with fetal size (Love and Kinch 1965, Griffiths et al. 2007), whereas maternal height is only weakly associated with birth weight (Kirchengast et al. 1998, Griffiths et al. 2007). The quality of the diet and the maternal ability to nourish the fetus properly are important factors affecting fetal growth (Carrera et al. 1998). Fetal genotype accounts for about 15% of the variation in birth weight (Carrera et al. 1998).

3.2.2 Fetal macrosomia

Definition

Fetal macrosomia is defined in many different ways in the literature, e.g. as an absolute birth-weight, over 4000 g or over 4500 g, or as a relative birth-weight, either above the 90th percentile or above +2 SD of the mean (97.7th percentile) of a standard population. Absolute birth weights are used when gestational ages are not known. Relative birth weights are preferable when the duration of pregnancy and fetal sex are known.

Prevalence

Fetal macrosomia complicates 30–50% of pregnancies in women with pregestational diabetes (Teramo 1998, Evers et al. 2004, Yang et al. 2006). It has been suggested that all fetuses of Type 1 diabetic mothers are actually 'macrosomic' (Bradley et al. 1988). These investigators observed that the birth-weight distribution of 280 consecutive offspring of Type 1 diabetic women was normally distributed, with the mean shifted to the right by 1.23 SDs compared with a standard population. There was a similar observation among 599 consecutive offspring of Type 1 diabetic women at Helsinki University Central Hospital (Teramo 1998).

Etiology

Both maternal diabetes and BMI are independently related to fetal growth (Ehrenberg et al. 2004). Pedersen's hypothesis states that fetal macrosomia is a

result of fetal hyperinsulinemia secondary to maternal and fetal hyperglycemia (Pedersen 1977c). This was confirmed by Susa et al. (1984) in a Rhesus monkey model. Continuous fetal insulin infusion without fetal hyperglycemia for 1–3 weeks in midgestation invariably resulted in fetal macrosomia and organomegaly (Susa et al. 1984). Fetal growth stimulation results from hyperinsulinemia, leading to increased deposition of fat. Insulin also stimulates amino acid uptake and tissue protein synthesis. Both clinical and experimental studies have shown that insulin is probably the most important fetal growth-promoting hormone (Hill 1982). Knip et al. (1983) showed that macrosomic infants of Type 1 diabetic women had a twofold increase in the concentrations of free insulin in cord blood when compared with normal weight infants of Type 1 mothers. Similarly, Schwartz et al. (1994) found that total and free insulin concentrations in fetal serum correlate positively with fetal macrosomia in diabetic pregnancies. In contrast, macrosomic fetuses of non-diabetic mothers are not hyperinsulinemic (Schwartz et al. 1994), which indicates that factors other than fetal hyperinsulinemia can also cause fetal overgrowth. Fetal hyperinsulinemia can also be endogenic, e.g. in the Beckwith-Wiedemann syndrome and nesidioblastosis of the fetal pancreas. In both of these syndromes the fetuses are typically macrosomic with visceromegaly and they may become severely hypoglycemic after birth (DeBaun et al. 2000, Best et al. 2006, Chen 2007).

Placental transfer of insulin complexed with antibodies has been suggested as a possible reason for fetal macrosomia (Knip et al. 1983, Menon et al. 1990). On the other hand, Schwartz et al. (1994) showed that women with Type 1 diabetes who do not have insulin antibodies have a similar rate of macrosomic infants compared with women who have insulin antibodies. Therefore, the importance of insulin antibodies in relation to fetal macrosomia remains uncertain.

Although fetal macrosomia is a result of maternal hyperglycemia, elevated levels of amino acids and lipids in the maternal circulation are also associated with fetal overgrowth (Hendrickse et al. 1985, Kliegmann and Gross 1985, Kalkhoff 1991). Fibroblast growth factor-2 (FGF-2) may also contribute to overgrowth in fetuses

of women with GDM (Hill et al. 1998). Insulin-like growth factor-1 (IGF-1) enhances placental amino acid transport (Karl 1995).

Maternal risk factors of fetal macrosomia

Both maternal obesity (Kirchengast et al. 1998, Shapiro et al. 2000, Ehrenberg et al. 2004, Yogev et al. 2005, Griffiths et al. 2007) and marked weight gain during pregnancy (Johnson et al. 1992, Kirchengast et al. 1998, Shapiro et al. 2000, DeVader et al. 2007) are important risk factors of fetal macrosomia. In a study of women with normal OGTT results, by Jensen et al. (2003a), the risk of macrosomia was significantly increased when the BMI was over 25 kg/m^2 compared with those with BMI under 25 kg/m^2. Women with a considerable weight gain during pregnancy have a 2- to 3-fold increased risk of delivering a large-for-gestational age (LGA) infant (Hedderson et al. 2006, DeVader et al. 2007). The risks of adverse maternal and fetal outcomes are lowest when maternal weight gain is optimal (Cedergren 2007). Low maternal gestational weight gain in obese women (less than 6 kg for women with a BMI of 30 kg/m^2 or more) has been shown to decrease the incidences of both maternal and fetal complications (Cedergren 2007).

Ethnicity has an effect on the occurrence of fetal macrosomia, both in the general population and in GDM pregnancies (Dornhorst et al. 1996, Rosenberg et al. 2003, Silva et al. 2006). Caucasian, Japanese and Chinese women have a lower risk of fetal macrosomia than native Hawaiin/Pacific-Islander and Filipino mothers (Silva et al. 2006). On the other hand, GDM has a greater influence on the birth-weight of Asian versus white European offspring (Dornhorst et al. 1996).

Although glycemic control among women with Type 1 diabetes has improved in recent decades, the rate of fetal macrosomia has not decreased (Persson and Hansson 1998, Teramo 1998). Large infants are associated with increased perinatal morbidity and mortality. Recently there has been a significant increase in mean birth-weight in both European (Surkan et al. 2004) and North American populations (Catalano 2007), possibly due to the world-wide obesity epidemic.

3.2.3 Intrauterine growth restriction

Intrauterine growth restriction (IUGR) is defined as a relative birth-weight below -2 SD of the mean birth-weight. An IUGR infant has, by definition, not reached his/her genetic growth potential *in utero* (Bamberg and Kalache 2004). Maternal pregestational diabetes mellitus may also be associated with IUGR, especially when retinopathy and nephropathy complicate diabetes (Reece et al. 1998). In patients with retinopathy and nephropathy, vascular adaptation of the placental bed is often insufficient, resulting in IUGR. In women with diabetic nephropathy, IUGR is observed in 15–21% of cases (Kitzmiller et al. 1981, Reece et al. 1998) compared with 3–10% in the normal population (Haram and Gjelland 2007).

Erythropoietin (EPO) is an endogenous hormone which controls the production of erythrocytes. The main stimulus to EPO production is low tissue oxygen concentration (hypoxia) (Marsden 2006). Teramo et al. (2004) reported that levels of amniotic fluid EPO correlate in a U-shaped fashion with fetal birth-weight z-scores in Type 1 diabetic pregnancies. Amniotic fluid EPO levels correlated inversely with the birth-weight z-score below -0.6 SD units, suggesting that these fetuses were actually growth restricted and that it was associated with chronic fetal hypoxia (Teramo et al. 2004).

3.3 Shoulder dystocia

3.3.1 General population

Shoulder dystocia can be defined as arrest of delivery after expulsion of the fetal head, although no general agreement has been reached (Gottlieb and Galan 2007). The incidence of shoulder dystocia varies widely, from 0.1 to 2.8% in unselected populations (Acker et al. 1985, Langer et al. 1991, Christoffersson and Rydhström 2002, Dandolu et al. 2005). Dandolu et al. (2005) reported that there was an increase in the rate of shoulder dystocia from 0.2% in 1979 to 2.1% in 2003. Both

excessive maternal weight before pregnancy and weight gain during pregnancy are associated with shoulder dystocia (Spellacy et al. 1985, Johnson et al. 1992). The incidence of shoulder dystocia is 3–13% in newborn infants with a birth weight of 4000 g or more (Benedetti and Gabbe 1978, Acker et al. 1985, Gross et al. 1987, Langer et al. 1991). In the study by Acker et al. (1985) the incidence of shoulder dystocia was 13% when the birth weight exceeded 4000 g, but only 1% when the birth weight was under 4000 g. In California, the percentages of births complicated by shoulder dystocia but not complicated by diabetes have been reported to be 5.2% for infants weighing 4000 to 4250 g, 9.1% for those weighing 4250 to 4500 g, 14.3% for those weighing 4500 to 4750 g and 21.1% for those weighing 4750 to 5000 g at birth (Nesbitt et al. 1998). Shoulder dystocia has been reported to occur in 40% of cases (31/78) when the birth-weight of vaginally delivered infants was at least 5700 g (Rydhström and Ingemarsson 1989).

3.3.2 Diabetic pregnancies

Large fetal size among women with GDM is a common risk factor for shoulder dystocia (Bennett 1999). Dystocia occurs more often in GDM pregnancies than in non-diabetic pregnancies, even when the birth weights are the same because of increased shoulder width. Any type of diabetes mellitus increases the risk of shoulder dystocia in vaginal deliveries (Acker 1985, Langer et al. 1991). Dandolu et al. (2005) observed an increased rate of shoulder dystocia both in GDM pregnancies (OR 1.9, 95% CI 1.7–2.3) and in pregnancies of women with pregestational diabetes (OR 3.8 95% CI 2.7–5.4). The risk of shoulder dystocia and trauma is further increased by the use of vacuum or forceps. In a study by Nesbitt et al. (1998) the risk of shoulder dystocia in cases of instrumentally assisted births among diabetic women was 12.2% for infants weighing 4000 to 4250 g, 16.7% for those weighing 4250 to 4500 g, 27.3% for those weighing 4500 to 4750 g and 34.8% for those weighing 4750 to 5000 g.

Insulin treatment in cases of GDM has been reported to decrease the rates of macrosomia (Roversi et al. 1980, Coustan and Imarah 1984, Langer 1993, Langer et al. 1994) and serious perinatal complications such as shoulder dystocia, bone fractures and brachial plexus nerve injury (Crowther et al. 2005). Langer et al. (2005b) reported a 2- to 4-fold increase in neonatal morbidity in cases of untreated GDM. They found an increased rate of macrosomia in the untreated GDM group. On the other hand, non-diabetic subjects and diet-treated or diet- and insulin-treated GDM patients had the same rate of macrosomia. In another study, Langer et al. (2005c) reported that an adverse pregnancy outcome was found in all women with GDM who had poor glucose control. On the other hand, obese women with GDM (BMI at least 30 kg/m^2) had pregnancy outcomes comparable with those among women with GDM and BMI <25 kg/m^2 when treated by means of diet and insulin but not by diet alone. They had a 2- to 3-fold risk of adverse outcome, despite acceptable glucose control with diet therapy. The outcome may thus be adverse even when glucose control is considered good. In a study among women with Type 1 diabetes, Evers et al. (2002b) showed that the incidence of fetal macrosomia was increased despite apparently good glycemic control throughout pregnancy.

Gestational diabetes mellitus has an unfavorable effect on fetal body composition (Neggers et al. 1995, Catalano et al. 2003). Newborn infants of women with GDM have increased fat mass compared with the infants of healthy women (Catalano et al. 2003). Fat deposition in the human fetus occurs mainly in the third trimester (Widdowson et al. 1972). Macrosomic infants of women with Type 1 diabetes (Pedersen 1977b) or GDM (Persson and Hanson 1998) also have organomegaly, e.g. enlargement of the liver and heart. The growth of these infants may be asymmetric, with larger shoulder/head and chest/head ratios than in the infants of non-diabetic women (Modanlou et al. 1982, Ballard et al. 1993).

3.4 Birth trauma

Shoulder dystocia and high birth-weight are the strongest risk factors as regards clavicular and other fractures and brachial plexus injury (Erb's palsy) (Levine et al. 1984, Mollberg et al. 2005). The incidence of brachial plexus injury is 0.15-0.3% (Gilbert et al. 1999, Mollberg et al. 2005, Backe et al. 2008). In an analysis of 66 086 births, Gregory et al. (1998) reported a brachial plexus injury rate of 0.1% among vaginally delivered infants weighing under 4000 g, but 0.9% when the birth weight was at least 4000 g. Similarly, others have reported rates of 0.6–1.1% for brachial plexus injury in vaginally-born infants weighing at least 4000 g among mothers without diabetes (Ecker et al. 1997, Kolderup et al. 1997, Bryant et al. 1998). The frequency of plexus injury was increased in the infants of women with GDM (OR 1.9, 95% CI 1.7–2.1) and in cases of vacuum extraction (OR 2.7, 95% CI 2.4–3.1) or forceps delivery (OR 3.4, 95% CI 2.7–4.3) (Gilbert et al. 1999). Diabetes increases the risk of brachial plexus injury by 2 to 5 times in infants weighing at least 4000 g at birth. In a Swedish study the overall perinatal mortality rate resulting from shoulder dystocia was 1.2%. It increased to 6.4% in mothers with diabetes mellitus (Christoffersson and Rydhström 2002).

Fracture of the clavicle occurs particularly during a difficult vaginal delivery, and especially when shoulder dystocia is present, or when the arms are extended in breech delivery. Fractures of the humerus (greenstick or full-thickness fracture) at birth are seen mostly when the newborn infant is macrosomic or is delivered vaginally in breech presentation (Caviglia et al. 2005). Fracture of the skull bones is associated with instrumental vaginal delivery (vacuum or forceps) and it may result in intracranial hemorrhage (Doumouchtsis and Arulkumaran 2008).

3.5 Fetal hypoxia

The incidence of abnormal fetal heart rate pattern during delivery, cord blood acidosis and low Apgar scores at birth is increased in diabetic pregnancies, indicating an increased risk of fetal hypoxia (Teramo et al. 1983, Mimouni et al.

1988, Salvesen et al. 1993, Casson et al. 1997). The exact mechanisms of fetal hypoxia are not fully understood. It is likely that several factors, alone or in combination, can result in decreased oxygen delivery to the fetus in diabetic pregnancies (Madsen 1986). Experimental and human studies have shown that both fetal hyperglycemia and hyperinsulinemia can independently cause fetal hypoxemia (Carson et al. 1980, Philipps et al. 1982, Milley et al. 1984, Widness et al. 1990). Elevated plasma and amniotic fluid EPO levels suggest that the fetuses of diabetic women can suffer from chronic hypoxia (Teramo et al. 1987, 2004). The iron stores in the fetal liver and brain are totally depleted in most cases of stillbirth in diabetic pregnancies reflecting increased erythropoiesis, further suggesting that these fetuses die from chronic hypoxia (Georgieff et al. 1992, Petry et al. 1992). Concentrations of maternal HbA_{1c} during the last weeks of pregnancy correlate directly with fetal cord plasma (Widness et al. 1990) and amniotic fluid EPO levels (Teramo et al. 2004), indicating that poor glycemic control during the last weeks of pregnancy increases the risk of intrauterine hypoxia. In a recent study of Type 1 diabetic pregnancies, the correlation between amniotic fluid EPO concentrations and birth-weight z-scores was U-shaped. Below a z-score of -0.6 SD units the correlation was negative but above +1.0 SD unit it was positive (Teramo et al. 2004). This suggests that the optimal birth-weight in Type 1 diabetic pregnancies is relatively narrow, and that fetal chronic hypoxia can occur when the birth-weight z-score is below -0.6 or above +1.0 SD unit.

3.6 Perinatal mortality

Perinatal mortality is in Finland defined according to WHO as a fetal death occurring at or after 22 weeks of gestation and/or ≥500 g birth-weight or a neonatal death occurring during the first 7 days of life. Perinatal mortality has decreased from 20–30% to under 5% during the last 50 years in pregnancies complicated by Type 1 diabetes mellitus (Schwartz and Teramo 2000, Gabbe and Graves 2003). However, it is still 3–5 times higher, even in centers specializing in the care of diabetic pregnancies, than the perinatal mortality rate in the general

population (Gabbe et al. 1977, Coustan et al. 1980, Jovanovic et al. 1981, Jensen et al. 2004, Macintosh et al. 2006, Bell et al. 2008). In Type 1 diabetic pregnancies the perinatal mortality rate ranges from 2.8 to 4.8% (Casson et al. 1997, Hawthorne et al. 1997, Platt et al. 2002, Penney et al. 2003, Evers et al. 2004). In a Danish nationwide prospective multicenter study the perinatal mortality was 3.1%, which was 4.1-fold higher than that in the background population (Jensen et al. 2004).

About 30 to 40% of perinatal deaths in Type 1 diabetic pregnancies are caused by malformations, and 20 to 30% by prematurity and intrauterine asphyxia, respectively (Schwartz and Teramo 2000). Stillbirths after 30 weeks of gestation form the majority of perinatal deaths in Type 1 diabetic pregnancies (Schwartz and Teramo 2000). Before 30 weeks, prematurity is the main cause of perinatal death (Teramo et al. 2005). In the 1950s, the risk of fetal death in Type 1 diabetic pregnancies was 5% at 32 weeks of gestation, increasing gradually to 15% at term (Hagbard 1956). Chronic fetal hypoxia is postulated to be the most likely reason for the majority of 'unexplained' stillbirths in diabetic pregnancies after 35 weeks of gestation (Schwartz and Teramo 2000).

There were 1365 consecutive childbirths from 1988 to 2006 at Helsinki University Central Hospital among women with pregestational diabetes, of which 96% had type 1 diabetes (Teramo et al. unpublished data 2007). Perinatal mortality was 1.9% (18 stillbirths and 8 neonatal deaths) during the study period (Table 1). The decrease in perinatal mortality is partially explained by the improved diagnosis of fetal malformations by sonography over the last 20 years. There were 12 induced abortions because of severe fetal malformations in women with pregestational diabetes during 1988–2006 at Helsinki University Central Hospital, of which at least 10 would have resulted in perinatal death. Thus, the total number of perinatal deaths would have been 36 (2.6%) instead of 26 (1.9%).

Table 1. Perinatal deaths in Type 1 diabetic pregnancies at the Department of Obstetrics and Gynecology, University Central Hospital, Helsinki, during 1988-2006

Case No.	White's class	Gestation (weeks+d)	Birth-weight		Perinatal death	Comment
			g	z-score		
1	B	23 + 5	575	..	F	PROM
2	C	25 + 1	370	- 5.0	F	Multiple malformations
3	C	25 + 1	500	- 4.4	N	RDS
4	B	25 + 2	725	- 2.8	N	RDS
5	B	26 + 0	440	- 4.5	F	Preeclampsia
6	D	26 + 1	650	- 2.8	F	IVF, twin B
7	C	26 + 3	830	- 1.5	F	Unexplained
8	F	26 + 4	785	- 2.1	N	RDS
9	C	27 + 6	400	- 5.3	F	Placental abruption
10	D	28 + 4	705	- 3.8	N	RDS
11	D	29 + 2	1195	- 1.3	F	Placental infarctions
12	F	30 + 1	810	- 3.9	N	RDS
13	F	30 + 1	1900	+1.7	N	Multiple malformations
14	B	31 + 1	1380	- 1.6	F	Cord complication
15	D	31 + 2	1255	- 2.4	F	Placental abruption
16	C	31 + 5	2160	+1.3	F	Maternal ketoacidosis
17	B	33 + 6	1350	- 3.4	F	Placental infarctions
18	B	34 + 4	2310	- 0.9	F	Unexplained, twin B
19	D	35 + 4	4100	+3.4	N	Severe shoulder dystocia
20	C	36 + 0	4030	+2.9	F	Unexplained
21	B	36 + 1	2250	- 1.8	F	Placental abruption
22	R	36 + 3	4630	+4.5	F	Unexplained
23	C	36 + 6	2290	- 0.5	F	Unexplained
24	B	37 + 3	6500	+7.8	F	Unexplained
25	D	38 + 1	3415	+0.2	F	Unexplained
26	D	39 + 2	5000	+3.0	N	Heart malformation

F = fetal; N = neonatal; PROM = premature rupture of membranes;
RDS = respiratory distress syndrome; IVF = in vitro fertilization

4. Neonatal complications

4.1 Hypoglycemia

Neonatal hypoglycemia is defined as a plasma glucose level below 2.6 mmol/l in a full-term infant (Cornblath et al. 2000). The prevalence of neonatal hypoglycemia ranges between 0.5 and 4% in infants born at term (Uvena-Celebrezze and Catalano 2000, Shand et al. 2008). Among the infants of women with GDM, hypoglycemia occurs in 6–19% (Langer et al. 2005, Shand et al. 2008) and in the pregnancies of pregestational diabetes (Type 1 or Type 2) the figure is 25–48% (Cordero et al. 1998, Evers et al. 2004, Shand et al. 2008). High amniotic fluid EPO levels obtained within 2 days before delivery can identify fetuses with an increased risk of neonatal hypoglycemia in Type 1 diabetic pregnancies (Teramo et al 2004). Neonatal hypoglycemia during the first days of life is a consequence of fetal hyperinsulinemia (Pedersen 1977b). A decreased ability to use glycogen and diminished hepatic glucose production in the first days of life predisposes newborn infants to hypoglycemia (Merlob and Hod 2008). Impaired counter-regulation by catecholamines may also have a role in the development of neonatal hypoglycemia (Schwartz and Teramo 2000). Most infants with neonatal hypoglycemia recover spontaneously, but symptomatic and prolonged hypoglycemia may result in permanent neurologic impairment or death (Armentrout and Caple 1999, Vannucci and Vannucci 2001).

4.2 Respiratory distress syndrome

The risk of respiratory distress syndrome (RDS) in newborn infants of Type 1 diabetic mothers is increased compared with that in the general population when matched for gestational age (Robert et al. 1976). Poor glycemic control during the last week of pregnancy has been shown to delay fetal lung maturation (Ylinen 1987), whereas the risk of RDS in infants of women with diabetes in good

glycemic control approaches that in the non-diabetic population (Kjos et al. 1990). Evaluation of fetal lung maturity by means of analysis of amniotic fluid has been recommended in insulin-treated diabetic pregnancies when an elective cesarean section is contemplated before the 38th gestational week (Hallman and Teramo 1979).

4.3 Polycythemia

Fetal polycythemia is defined as cord blood hematocrit at or above 65% at birth. The occurrence of polycythemia is increased in infants of diabetic mothers (Salvesen et al. 1992). These infants have polycythemia up to five times more often than infants of non-diabetic women (Mimouni et al. 1986). Fetal polycythemia is a result of accelerated erythropoietin-induced red blood cell production in response to chronic fetal hypoxia (Shannon et al. 1986, Widness et al. 1990, Teramo and Widness 2008). Polycythemia may lead to hyperviscosity syndrome and fetal renal vein thrombosis (Avery et al. 1957, Hibbert et al. 1997).

4.4 Hyperbilirubinemia

The definition of neonatal hyperbilirubinemia is complicated. Both gestational age and the age of the newborn infant are related to serum bilirubin levels. A serum bilirubin concentration exceeding 205–222 μmol/l in term infants is considered abnormally high (Maisels 1992). Hyperbilirubinemia complicates up to 20% of the newborn infants of women with GDM compared with 10% in the general population (Uvena-Celebrezze and Catalano 2000). Hyperbilirubinemia has been reported in 24 to 45% of the newborn infants of Type 1 diabetic pregnancies (Teramo et al. 1979, Cordero et al. 1998). The etiology of the increased frequency of hyperbilirubinemia in diabetic pregnancies is not fully understood. It may be due to delayed clearance of bilirubin in newborn infants of diabetic mothers (Stevenson et al. 1987). In addition, polycythemia contributes to

hyperbilirubinemia because of the increased amount of breakdown products (Merlob and Hod 2008).

4.5 Hypocalcemia and hypomagnesemia

Hypocalcemia and hypomagnesemia in infants of diabetic mothers are clinically less important than other neonatal complications. Maternal magnesium and parathyroid hormone concentrations are decreased in diabetic women, which may result in fetal hypomagnesemia (Uvena-Celebrezze and Catalano 2000) and this in turn can lead to reduced concentrations of fetal parathyroid hormone and hypocalcemia. Neonatal hypocalcemia is defined as an ionized serum calcium level below 1.05 mmol/l and hypomagnesemia as a plasma magnesium level of less than 0.5 mmol/l. Hypocalcemia affects 18–32% of infants born to Type 1 diabetic women (Teramo et al. 1979, Demarini et al. 1994). The severity of hypocalcemia has been reported to correlate with the degree of glycemic control during pregnancy (Tsang et al. 1975, Demarini et al. 1994).

4.6 Obstructive cardiomyopathy

Fetuses of women with pregestational diabetes have an increased risk of developing cardiac septal hypertrophy (Walther et al. 1985, Vela-Huerta et al. 2000). This may be due to fetal chronic hypoxia as indicated by elevated amniotic fluid EPO levels (Teramo and Widness 2008). Newborn infants with obstructive cardiomyopathy often have cyanosis or cardiac failure during the first days of life (Gutgesell and Speer 1980). On the other hand, infants with cardiomyopathy may remain asymptomatic during the newborn period, and regression to normal tends to occur by 3–6 months of age (Merlob and Hod 2008).

AIMS OF THE STUDY

The present study was undertaken to investigate maternal and fetal outcomes in pregnancies complicated by gestational or Type 1 diabetes mellitus.

The specific aims of the study were:

1. to clarify the relationship between glucose control and pregnancy-induced hypertension and preeclampsia in women with GDM

2. to study the ability of the 2-hour oral glucose tolerance test combined with the 24-hour glucose profile to distinguish between low and high risks of fetal macrosomia in GDM pregnancies

3. to assess the effect of glucose control on the risk of fetal malformations in women with Type 1 diabetes

4. to study the risk of pregnancy-induced hypertension and preeclampsia in relation to glucose control in women with Type 1 diabetes

SUBJECTS AND METHODS

Subjects

A total of 986 women with GDM and 203 women with borderline glucose intolerance (one abnormal value in the OGTT) with a singleton pregnancy, 488 pregnant women with Type 1 diabetes (691 pregnancies and 709 offspring), and 1154 pregnant non-diabetic women (1181 pregnancies and 1187 offspring) at Helsinki University Central Hospital were investigated. The study protocols were approved by the local ethics committee (Studies I–IV) and the Ministry for Social Affairs and Health (Studies II–IV).

Study I

All 284 consecutive women with gestational glucose intolerance and singleton childbirth (81 women with GDM and 203 women with borderline glucose intolerance) between April 1, 1987 and March 31, 1988 at Helsinki University Central Hospital were prospectively studied for pregnancy complications and perinatal outcome. Control subjects consisted of 327 healthy women with normal OGTT results at 28–32 weeks of gestation and with singleton childbirth at the same hospital during the same time period. These control subjects were population-based and participated in another study in which all pregnant women underwent OGTTs.

Study II

This study included 520 diet-treated and 385 insulin- and diet-treated women with GDM and singleton childbirth at Helsinki University Central Hospital during 1988–1997. These two GDM cohorts were studied retrospectively to assess the effects of hyperglycemia and other factors on fetal macrosomia and birth trauma. If a woman had two or more childbirths during the study years, only the last pregnancy was included in the study. The control group consisted of 805 non-diabetic women residing in the town of Kerava (near Helsinki), who participated

in routine ultrasosonography screening at 16–19 weeks of gestation and who had a singleton childbirth during 1993–95.

Study III

In order to assess the relationship between glycemic control in early pregnancy and the risk of congenital malformations, 691 consecutive pregnancies in 488 women with Type 1 diabetes and their 709 offspring were studied between 1988 and 1997 at Helsinki University Central Hospital. Control subjects consisted of 735 newborn infants from 729 consecutive pregnancies of 709 non-diabetic women from the town of Kerava, who attended routine ultrasonographic screening at 16–19 weeks of gestation, with childbirth at Helsinki University Central Hospital in 1993–1995.

Study IV

From the same study and control subjects as in the malformation study (Study III), 683 Type 1 diabetic pregnancies in 480 women and 854 pregnancies in 827 control women with childbirth at Helsinki University Central Hospital (residents of Kerava) were followed throughout pregnancy in order to evaluate the possible relationship between glycemic control and hypertensive pregnancy complications.

Methods

1. Screening, diagnosis and treatment of gestational diabetes mellitus

The data of the women and their newborns were collected from patient records. In the catchment area of Helsinki University Central Hospital, all pregnant women with at least one risk factor for GDM (Table 2) underwent a 2-hour oral glucose tolerance test (OGTT). The test was normally performed at 24–28 weeks of

pregnancy, and earlier when indicated. About 30% of Finnish pregnant women have at least one of risk factor for GDM (Hyvönen 1991).

Table 2. The 2-hour oral glucose tolerance test (OGTT) with 75 g of glucose was done in patients with one or more of the following risk factors

Family history of diabetes
GDM in previous pregnancy
Prepregnancy BMI >25 kg/m^2
Age ≥40 years
Glucosuria in current pregnancy
Birth-weight >2 SD-units or >4500 g in previous pregnancy
Suspicion of fetal macrosomia in current pregnancy
Previous infant with hypoglycemia or major malformation
Previous unexplained stillbirth or neonatal death

The 2-hour OGTT was carried out with 75 g of glucose after a 12-hour overnight fasting. Samples for plasma glucose measurements were obtained immediately before (fasting value) and at 1 and 2 hours after the 75 g glucose load. The results were considered abnormal if any of the three plasma glucose values equalled or exceeded the 97.7th percentile value derived from a Finnish control population (Hyvönen 1991). The 97.7th percentile values were 5.1 mmol/l at 0 hour, 10.0 mmol/l at 1 hour and 8.7 mmol/l at 2 hours. In the present study the diagnosis of GDM was made when 2 or 3 values of the 2-hour OGTT were abnormal. Patients with only one abnormal value in the OGTT were considered to have borderline glucose intolerance.

Women with an abnormal OGTT result received dietary counseling aiming at normoglycemia. Within one week, women with two or three abnormal values had a 24-hour glucose profile carried out in the hospital with samples taken at 4-hour intervals, i.e. a total of 7 plasma glucose measurements. The measurements were done at 8.00, 12.00, 16.00, 20.00, 24.00, 04.00, and 08.00 o'clock. The

measurements at 12.00 and 20.00 o'clock were postprandial. In Study I, women with one abnormal glucose value in the OGTT also underwent a 24-hour glucose profile. Insulin treatment was started with a single dose of 8–16 units of NPH insulin daily, usually in the evening in addition to the diet, when two fasting values were at least 5.5 mmol/l, or one fasting value was at least 5.5 and one postprandial value at least 7.8 mmol/l. Women with GDM and on insulin treatment measured their blood glucose at home 5 times a day, 2 to 3 days a week. Insulin-treated GDM patients were followed at the outpatient maternity clinic at 2- to 4-week intervals. Women with only one abnormal OGTT value were followed at the maternity health care centers. Their fasting plasma glucose levels were measured at 2- to 4-week intervals. As long as the fasting plasma glucose level remained under 5.5 mmol/l, diet therapy was considered sufficient. When diet alone failed to achieve normoglycemia, the 24-hour glucose profile was done as described above.

2. Follow-up and treatment of Type 1 diabetic pregnancies

Pre-pregnancy planning and care was recommended to all women with pregestational diabetes. However, only 40% of the Type 1 diabetic women were seen in the outpatient maternity clinic of this hospital. Of the remaining 60%, many had been counseled by their family doctor or a diabetologist, but their exact number is not known.

Women with Type 1 diabetes attended the outpatient maternity clinic of this hospital at 2-to 6-week intervals during the first two trimesters and more frequently during the third trimester. They were advised to measure their blood glucose concentration at home as described above for women with insulin-treated GDM. A long acting NPH insulin preparation was administered once or twice daily. In addition, a short-acting insulin preparation was used at meals, in most patients three or four times a day. Consultation with a dietician was arranged in early pregnancy and later when needed. Retinal examination was carried out done

by an ophthalmologist in early pregnancy if the last evaluation of the retina had preceded the pregnancy by more than 6 months. The first ultrasonography was performed in early pregnancy and after that carried out every 4–8 weeks. For detection of major fetal malformations a comprehensive ultrasonographic examination was performed by a perinatologist at 16–20 weeks of gestation. Monitoring by cardiotocography was carried out at each visit after 28 weeks of gestation and after 34 weeks also between visits as needed. The patients routinely underwent amniocentesis for evaluation of fetal lung maturity, at the latest at 37 completed weeks of pregnancy or earlier if complications appeared. In diabetic pregnancies, the fetal lungs were considered functionally mature when the lecithin/sphingomyelin ratio was >2 and phosphatidylglycerol was detected in the amniotic fluid (Hallman and Teramo 1979, Hallman et al 1980). Labor was induced or elective cesarean section performed when fetal lung maturity was demonstrated in the amniotic fluid. Elective cesarean section was preferred in patients of White's classes D, R or F. Indications for cesarean section delivery were fetal macrosomia or signs of fetal distress.

3. Blood pressure measurement and evaluation of proteinuria

Blood pressure was measured after 10-15 minutes' rest with the subject in a sitting or semi-recumbent position with a mercury sphygmomanometer. The diastolic blood pressure level was obtained from the Korotkoff phase V (disappearance of sounds). The measurements were carried out as part of the routine clinical follow-up by midwives and nurses. Blood pressure during pregnancy was considered increased if the following two criteria were met at two sessions at least 24 h apart: (1) diastolic pressure increased by 15 mmHg or more from the first measurement during pregnancy until the end of pregnancy, and (2) the final level reached 90 mmHg or more. In the analyses, the second highest blood pressure value was used.

Urine was checked for protein by a semi-quantitative dipstick method at each clinical visit. Results of '++' or repeated '+' were confirmed by way of a quantitative analysis. A diagnosis of proteinuria was made if the amount of protein excretion was 0.3 g or more/24 h.

Chronic hypertension was defined as diastolic blood pressure of more than 90 mmHg repeatedly in the first trimester. Pregnancy-induced hypertension was defined as diastolic blood pressure of 90 mmHg or more repeatedly after 20 weeks of gestation in previously nonhypertensive women. Preeclampsia was defined as PIH with proteinuria of 0.3 g/24 h or more (Study IV). In Study I both preeclampsia and PIH were defined as diastolic blood pressure of more than 90 mmHg repeatedly after 20 weeks of gestation.

4. Plasma glucose measurement

In Study I plasma glucose was determined using a photometric hexokinase method (Kone Specific, Espoo, Finland). In Studies II–IV plasma glucose was measured by means of a glucose oxidase electrode with amperometric detection (ESAT 6660®, Eppendorf, Hamburg, Germany).

5. Assessment of long-term glycemic control

Concentrations of glycated hemoglobin were assessed (as HbA_{1c}) by means of an HPLC method (Diamat®, Bio-Rad Laboratories, Hercules, California, USA) at the first visit of Type 1 diabetic women to the maternity outpatient clinic and thereafter every 4 to 6 weeks until delivery. Using this method, the mean HbA_{1c} value is 4.93% (SD 0.32) in healthy non-diabetic Finnish adults. Values less than 5.6% (mean + 2 SD) were considered normal.

In Study IV three values of HbA_{1c} were selected as follows: the first measurement in the first trimester, the second at 22 weeks of gestation and the third the last measurement before delivery. The first HbA_{1c} assessment was carried out at 7 weeks of gestation (median) and in 93% of the women by the end of the 14th week. For the mid-pregnancy measurement, the value obtained closest to 22 weeks was used (range 20–25 weeks). The last measurement before delivery was obtained at 2 weeks before delivery (median, range 0–4 weeks).

6. Assessment of the health of the newborn infant

After delivery, the infants of diabetic mothers were observed for at least two hours at the labor and delivery ward. Newborn infants were transferred to the neonatal intensive care unit in cases of respiratory distress, neonatal hypoglycemia, or difficulties in adaptation after delivery. Blood glucose was measured four times during the first day of life and later as indicated in infants of Type 1 and GDM pregnancies. Neonatal hypoglycemia was defined as a blood glucose concentration below 1.8 mmol/l at least twice and at least one of these after six hours of age (Study I). Neonatal hyperbilirubinemia was considered present when bluelight phototherapy or exchange transfusions were indicated. Relative birth-weight (standardized for gestational age and fetal sex) was expressed as standard deviation units (z-scores) using a large Finnish standard population as reference (Pihkala et al 1989). The newborn infant was considered macrosomic if the birth-weight was more than 2.0 SD-units (97.7th percentile). The frequency of infants with a birth-weight over the 90th percentile was also calculated in GDM pregnancies for comparison (Study II). Infants of women with diabetes and control subjects were examined by a neonatologist after birth and at 2–5 days of age at discharge from the hospital. A malformation was classified as ‘major’ if it was fatal, likely to cause a serious handicap, or if it required surgery. Other malformations were classified as ‘minor’, which included undescended testis, hydrocele of the scrotum and dislocation of the hip. Each offspring was classified according to the most serious disorder as having either major, minor, or no

malformation (Study III). Erb's palsy was diagnosed by a pediatric surgeon (Study II).

7. Statistical analyses

For continuous variables, Student's *t*-test and the Mann-Whitney *U*-test were used to compare two groups. For more than two groups, comparisons were carried out by way of one-way ANOVA and the Bonferroni procedure, or by way of the Kruskal-Wallis test. Categorial data and proportions were compared either with the Chi-square test (with Yates' correction as needed), or by calculating the rate difference and its 95% CI. Trends in proportions were evaluated by the Armitage test. Fisher's exact probability test was used for small numbers when appropriate. Relative risks or odds ratios with 95% CIs were calculated for different risk factors. Multiple logistic regression was used to identify variables independently associated with the outcome. All tests were two-sided. Values of p less than 0.05 were considered statistically significant. Calculations were performed using Arcus Quickstat Biomedical (Longman Software Publishing, Cambridge, UK) and the NCSS 2000 software (NCSS Inc., Kaysville, Utah, USA).

RESULTS

1. Pregnancy-induced hypertension, preeclampsia and gestational diabetes mellitus (Study I)

1.1 Maternal clinical data

Women with GDM and with two or three abnormal values in the OGTT (GDM group) were older than the control women and their pre-pregnancy BMIs were higher than the BMIs of the controls (Table 3). Women with one abnormal value in the OGTT (borderline group) also had higher BMIs than the controls. However, weight gain during pregnancy was lowest in the women with GDM (Table 3). These women had almost twice as many cesarean section deliveries than the controls.

Table 3. Maternal data (mean and SD or frequency) of women with gestational diabetes (GDM), of women with one abnormal value in the OGTT (borderline glucose intolerance), and of non-diabetic healthy pregnant women (controls) (Study I)

	Controls	Glucose intolerance	
		Borderline	GDM
Number of women	327	203	81
Maternal age (years)	31.2 (4.6)	32.2 (5.2)	33.2 (5.5)[a]
Pre-pregnancy weight (kg)	59.3 (8.8)	62.8 (12.6)[a]	68.0 (14.5)[b]
Body mass index (kg/m^2)	21.8 (2.9)	23.4 (4.3)[b]	25.5 (5.1)[b]
Pregnancy weight gain (kg)	14.0 (3.7)	13.3 (5.2)	10.6 (5.3)[b]
Cesarean sections (%)	53 (16.2)	44 (21.7)	25 (30.9)[a]

[a]$p<0.01$, [b]$p<0.001$, compared with controls

1.2 Frequency of hypertensive pregnancy complications

The frequency of hypertensive pregnancy complications was higher in the GDM patients (two or three abnormal values in the OGTT) than in the non-diabetic controls (19.8% vs. 6.1%, $p<0.001$). The frequency of chronic hypertension was also higher in the GDM women than in the controls (2.5% vs. 0.3%, $p<0.05$). Women with borderline glucose intolerance (one abnormal value in the OGTT) had the same frequency of hypertensive complications as the controls.

2. Fetal macrosomia and gestational diabetes mellitus (Study II)

2.1 Maternal characteristics

Of the 905 GDM women, 520 (57.5%) were treated by means of diet only and 385 (42.5%) by means of diet and insulin. Both the diet- and diet plus insulin-treated GDM patients were older and more obese and had previously given birth more often to a newborn infant weighing >4000 g than the non-diabetic controls (Table 4). The insulin-treated GDM women had more childbirths than the controls, whereas the diet-treated women had the same mean parity as the controls. The cesarean section rate was more than twice as high in the insulin-treated GDM patients versus the controls.

Table 4. Maternal characteristics of women with GDM and of healthy controls. Values are means (SD) or frequencies (Study II)

	Controls	GDM, diet only	GDM, diet + insulin	p
Number of women	805	520	385	
Nulliparous (%)	332 (41.2)	187 (36.0)	91 (23.6)	<0.001[b]
Age (years)	29.5 (5.0)	33.5 (5.4)	34.0 (5.4)	<0.001[a]
Body mass index (kg/m^2)	23.1 (3.9)	26.1 (5.4)	29.0 (6.8)	<0.001[a]
Cesarean section (%)	150 (18.6)	140 (26.9)	163 (42.3)	<0.001[a]
Previous child's birth-weight >4000 g (%)	72 (8.9)	99 (19.0)	128 (33.2)	<0.001[a]

[a]Both GDM groups differ from controls

[b]Insulin-treated GDM group differs from controls and diet-treated GDM group

2.2 Neonatal outcome

Fetal macrosomia occurred more often in the insulin-treated GDM pregnancies (18.2%, p<0.001) than in the diet-treated GDM pregnancies (4.4%) or the controls (2.2%) (Table 5). However, the number of newborn infants with a birth-weight over the 90th percentile was significantly higher in the diet-treated GDM pregnancies than in the controls (Table 5). The rate of Erb's palsy in vaginally delivered infants was 2.7% in the insulin-treated group and 2.4% in the diet-treated group. Both frequencies were significantly higher than in the controls (0.3%, p<0.001).

Table 5. Clinical data of the newborn infants of women with GDM and of healthy controls. Values are means (SD) or frequencies (%) (Study II)

	Controls	GDM, diet only	GDM, diet + insulin	p
Number of newborn infants	805	520	385	
Gestational age (days)	278 (13)	277 (11)	265 (11)	<0.001[b]
Birth-weight (g)	3517 (570)	3616 (580)	3624 (677)	<0.001[a]
Birth-weight z-score				
>2 SD-units (>97.7th percentile)	18 (2.2)	23 (4.4)	70 (18.2)	<0.001[b]
Birth-weight >90th percentile	70 (8.7)	77 (14.8)	143 (37.1)	<0.001[a]
Erb's palsy in vaginal deliveries (%)	2 (0.3)	9 (2.4)	6 (2.7)	<0.001[a]

[a]Both GDM groups differ from controls

[b]Insulin-treated GDM group differs from controls and diet-treated GDM group

2.3 Fetal macrosomia and pre-pregnancy BMI

The proportion of macrosomic newborn infants was highest in insulin-treated GDM patients even when the maternal BMI was under 25 kg/m^2 (Figure 1). However, the prevalence of fetal macrosomia was more than twice as high (24.7% vs. 11.9%) in obese (BMI at least 30 kg/m^2) than in non-obese (BMI <25 kg/m^2) insulin-treated GDM patients.

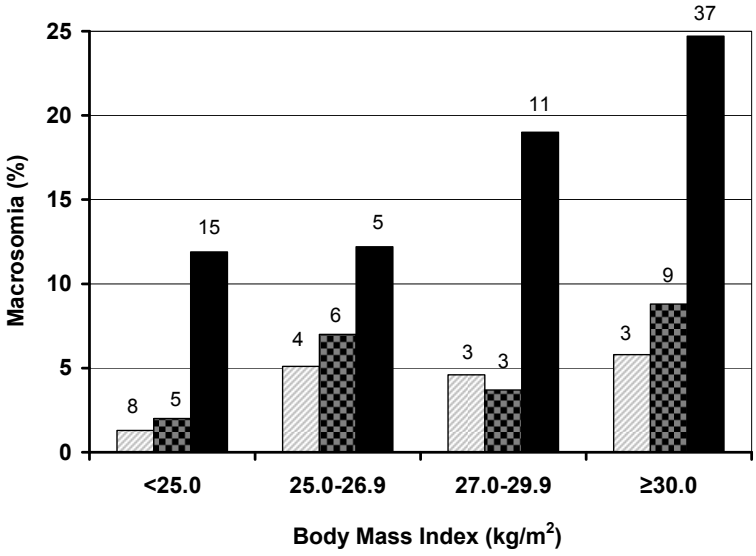

Figure 1. Frequency of macrosomia as a function of pre-pregnancy BMI in non-diabetic controls (grey columns) and in diet-treated (checkered columns) and insulin-treated (black columns) women with GDM. The numbers above the columns indicate the numbers of macrosomic newborn infants.

2.4 Fetal macrosomia and the 2-hour oral glucose tolerance test

When the women with GDM were grouped according to their 2-hour plasma glucose values in the OGTT, the frequency of macrosomia was significantly higher in all groups than in the controls, even when the 2-hour value was below 7.8 mmol/l (Figure 2). In contrast, the fasting value in the 2-hour OGTT of the same GDM women correlated well with the frequency of macrosomia (Figure 3).

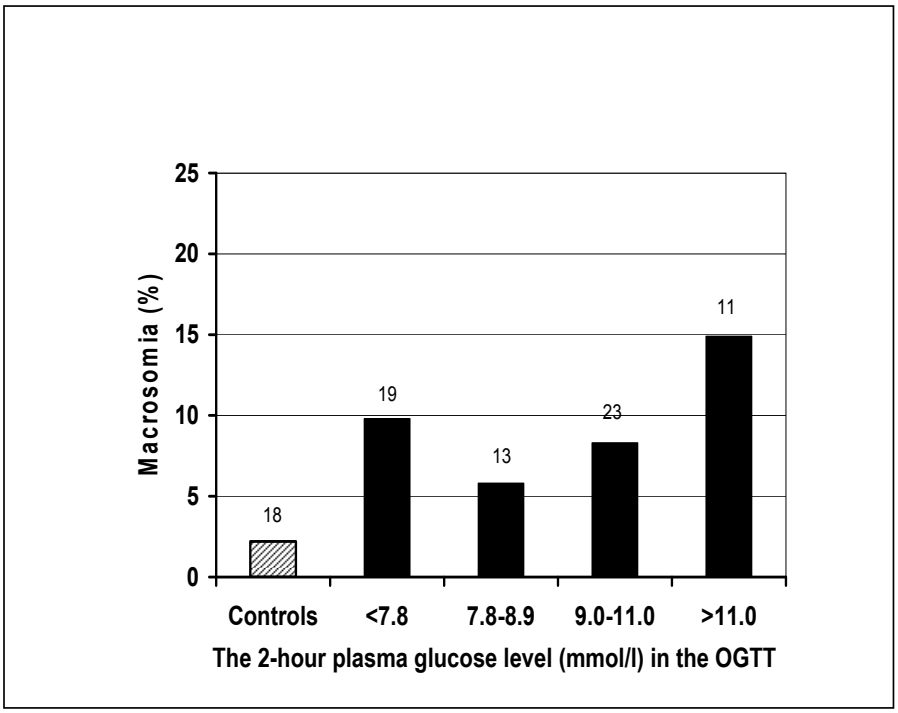

Figure 2. Distribution of 66 macrosomic newborn infants of 782 women with GDM as a function of the 2-hour plasma glucose level in the OGTT (black columns). The frequency of macrosomia in the controls is also shown for comparison (grey column). There was no significant trend among the GDM patients. The numbers above the columns indicate the numbers of macrosomic newborn infants.

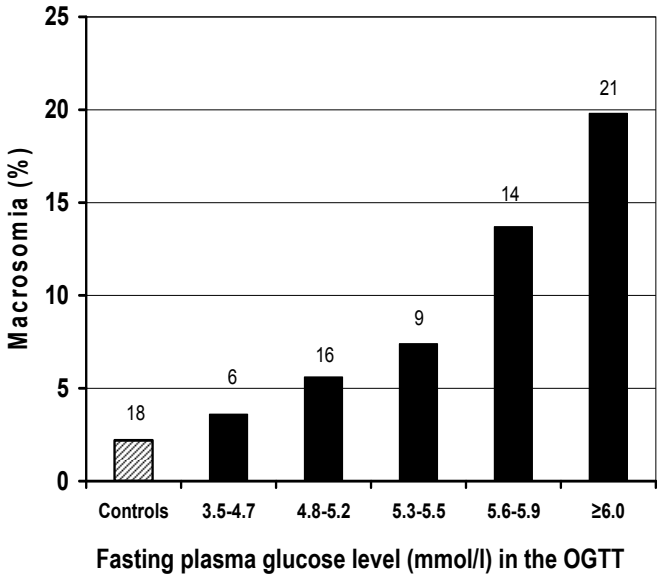

Figure 3. Distribution of 66 macrosomic newborn infants of 782 women with GDM as a function of the fasting plasma glucose level in the 2-hour OGTT (black columns). The frequency of macrosomia in the non-diabetic controls is also shown for comparison (grey column). The trend among the GDM patients was highly significant ($p<0.001$). The numbers above the columns indicate the numbers of macrosomic newborn infants.

3. Congenital malformations in pregnancies with Type 1 diabetes (Study III)

3.1 Frequency and type of fetal malformations

A major fetal malformation was observed in 30 (4.2%) of the 709 offspring in Type 1 diabetic women and in 10 (1.4%) of the 735 control offspring (RR 3.1; 95% CI 1.6–6.2). The corresponding frequencies of minor malformations were 6.1% among Type 1 diabetic pregnancies and 3.0% among the controls. The combined frequencies of major and minor malformations were 10.3% in diabetic pregnancies and 4.4% in the controls.

Cardiovascular malformations (12/30) were the most common type of major malformation in the diabetic pregnancies. Musculo-skeletal (6/30), central nervous system (4/30) and gastrointestinal malformations (4/30) were also common among the major malformations. Induced abortion because of a major fetal malformation was carried out in five of the Type 1 diabetic and in none of the control pregnancies.

3.2 Glycemic control and fetal malformations

The relative risk of major malformation was 3.0 (95% CI 1.2–7.5) when comparing Type 1 diabetic women with non-diabetic controls, even in those diabetic women whose HbA_{1c} level was only slightly increased (by 2.0 to 5.9 SD-units) (Table 6). Only diabetic women with normal HbA_{1c} levels (less than 5.6%) had the same low risk as the control subjects. The mean maternal HbA_{1c} level was 6.4% in those infants with a central nervous system malformation and 7.6% in those with a cardiovascular malformation.

Table 6. Hemoglobin A1c in early pregnancy in women with Type 1 diabetes and the risk of major fetal malformations compared with non-diabetic control subjects (Study III)

First trimester HbA1c (%)	SD-units	No. of offspring with malformation	Relative risk (95% CI)
<5.6	<2.0	1/47	
5.6-6.8	2.0-5.9	7/170	3.0 (1.2-7.5)
6.9-8.0	6.0-9.9	8/252	2.3 (1.0-5.7)
8.1-9.3	10.0-13.9	6/133	3.3 (1.3-8.6)
≥9.4	≥14.0	4/61	4.8 (1.6-13.9)
Unknown	Unknown	4/49	6.0 (2.0-17.1)
Offspring of diabetic women		30/709	3.1 (1.6-6.2)
Control offspring		10/735	1.0

4. Hypertension and glycemic control in Type 1 diabetic pregnancies (Study IV)

4.1 Glycemic control

Preeclampsia was diagnosed in 12.8% of the women with Type 1 diabetes (excluding those with pre-pregnancy nephropathy) and in 2.7% of the control women (OR 5.2; 95% CI 3.3–8.4). A positive correlation was observed between the HbA_{1c} level in early pregnancy and the occurrence of preeclampsia (Table 7). Pregnancy-induced hypertension was observed in 11.4% of the diabetic women (excluding those with pre-pregnancy nephropathy), compared with 5.6% of the control women (OR 2.2, 95% CI 1.5–3.1). Unlike preeclampsia, no association between HbA_{1c} values and the occurrence of PIH was observed (Table 7).

Table 7. Frequency of preeclampsia and PIH in Type 1 diabetic women without diabetic nephropathy grouped according to HbA_{1c} level and in control subjects (Study IV)

HbA_{1c} in early pregnancy	Total number	Preeclampsia [a]		PIH	
		Number	%	Number	%
<5.6%	41	2	4.9	4	9.8
5.6-6.8%	154	11	7.1	14	9.1
6.9-8.0%	221	30	13.6	31	14.0
>8.0%	171	34	19.8	16	9.4
Unknown	29	2	6.9	5	17.2
Non-diabetic controls	854	23	2.7	48	5.6

[a] Armitage test for trend p<0.001

4.2 Risk factors of preeclampsia

Glycemic control, nulliparity, diabetic retinopathy and duration of diabetes were statistically significant independent predictors of preeclampsia calculated by multiple logistic regression analysis (Table 8). The adjusted odds ratios for preeclampsia were 1.6 (95% CI 1.3–2.0) for each 1% unit increment in the HbA_{1c} value during the first trimester and 0.6 (95% CI 0.5–0.8) for each 1% unit decrement achieved during the first half of pregnancy. Changes in glycemic control during the second half of pregnancy did not alter the risk of preeclampsia. Of the 67 patients with pre-pregnancy nephropathy, 38 (57%) had preeclampsia or PIH on the basis of the blood pressure criteria and urinary protein excretion.

Table 8. Factors associated with preeclampsia in 616 Type 1 diabetic women without diabetic nephropathy (Study IV)

	Unadjusted		Adjusted		
	OR	**95% CI**	**OR**	**95% CI**	**p**
Nulliparity	2.9	1.9-4.5	2.7	1.7-4.3	<0.0001
Retinopathy	3.0	2.0-4.5	2.0	1.2-3.3	0.0001
Duration of diabetes	1.3[a]	1.2-1.5	1.2[a]	1.0-1.5	0.02
HbA_{1c} in early pregnancy	1.3[b]	1.1-1.5	1.6[b]	1.3-2.0	<0.0001
HbA_{1c} improvement until mid-pregnancy	1.0[c]	0.9-1.2	0.6[c]	0.5-0.8	<0.0001

[a] Increase of risk for each additional 5 years duration of diabetes
[b] Increase of risk for each 1% unit increment of HbA_{1c}
[c] Reduction of risk for each 1% unit decrement of HbA_{1c}

DISCUSSION

1. Gestational diabetes mellitus

1.1 Screening and diagnosis

The main purpose of screening for GDM is to find the women with a high risk of maternal and perinatal complications. The prevalence of GDM has been increasing in recent decades (Ferrara et al. 2004, Dabelea et al. 2005). Therefore, it is a growing challenge to detect pregnancies at risk of GDM as early as possible during pregnancy. The best strategy would be to prevent the occurrence of GDM, but no controlled studies on GDM prevention have been published so far.

The diagnosis of GDM is based on the results of a glucose tolerance test carried out either with a 75 or 100 g glucose load. The 75 g OGTT is carried out as a 2-hour test whereas the 100 g OGTT is a 3-hour test (Metzger and Coustan 1998). The cut-off levels as regards abnormal values differ considerably in different countries and they have also been changing during the last 30 years. The cut-off plasma glucose values of the 2-hour OGTT recommended by the 4th Workshop-Conference on GDM and the American Diabetes Association are 5.3, 10.0 and 8.6 mmol/l for the fasting, 1-hour and 2-hour values, respectively (Metzger and Coustan 1998, American Diabetes Association 2004). These cut-off values have recently been adopted as the new recommendations for GDM screening and diagnosis in Finland (The Finnish Working Group on Gestational Diabetes 2008). In the present study the cut-off plasma glucose values used for the diagnosis of GDM were based on the results of a large population-based Finnish study (Hyvönen 1991). These values differ only slightly from those recommended by the 4th Workshop-Conference on GDM (Metzger and Coustan 1998).

The fact that no consensus has been reached on how to screen for GDM suggests that no single screening method has been considered superior. Recently, it has

been suggested that almost all pregnant women should be screened for GDM (Kaaja and Rönnemaa 2008). Only women considered to have a very low risk do not need to be screened. However, the possible benefits of the universal screening for GDM have so far not been sufficiently studied. By way of the screening method used in the present study, combined with a 24-hour glucose profile, we could separate GDM pregnancies at high and low risks of fetal macrosomia. Those who needed insulin therapy had a high risk of fetal macrosomia. To our knowledge no other method for detection of high risk GDM pregnancies has been as efficient as the present study.

The results of previous studies (Nord et al. 1995, Jensen et al. 2003b, Berg et al. 2007) and those of the present study (II) show that the degree of the severity of GDM, as indicated by high blood glucose values and the need of insulin treatment, clearly influences the complication rates. The results of a recent large multicenter study indicated that no clear cut-off levels exist for any of the 2-hour OGTT plasma glucose values above which perinatal complications are markedly increased (Metzger et al. HAPO 2008). Therefore, the cut-off values of plasma glucose levels in the diagnosis of GDM are arbitrary. No general agreement has been reached in defining the diagnostic cut-off levels for GDM.

1.2 Preeclampsia and pregnancy-induced hypertension

Preeclampsia and PIH occurred significantly more frequently in the women with GDM than in the controls (Study I), which is in agreement with most other studies (Nordlander et al. 1989, Persson and Hanson 1998, Starcevic and Djelmis 2004, Östlund et al. 2004, Hunger-Dathe et al. 2005). In women with GDM the rate of preeclampsia is 2.0 to 3.3 times greater than in non-diabetic controls. In the present work (Study I) the rate of preeclampsia and PIH in GDM women was 3.2 times higher than in the healthy controls. Furthermore, the incidence of obesity was higher in the patients with GDM than in the healthy controls, which also contributed to the increased risk of preeclampsia and PIH. At least one group of investigators has found no increase in pregnancy-induced hypertensive disorders

in GDM pregnancies (Schaffir et al. 1995). Although an increased risk of preeclampsia has been reported in women with mild glucose intolerance (only one abnormal value in the OGTT) (Lindsay et al.1989), our work (Study I) did not show such an association. In a study by Ros et al. (1998) GDM was associated with an increased risk of preeclampsia, but the risk of PIH was not increased.

1.3 Fetal macrosomia

Fetal macrosomia is one of the main complications of GDM pregnancies and it can result in both maternal and perinatal birth trauma, perinatal hypoxia and even fetal death. The definition of macrosomia used in the present work (Studies I and II; birth-weight z-score > +2.0 SD-units) is relatively strict. In many studies fetal macrosomia is defined as a birth- weight >90th percentile of a reference population. The +2.0 SD above the mean corresponds to the 97.7th percentile in a normally distributed cohort. Fetal macrosomia occurred in 18.2% of insulin-treated GDM pregnancies when > +2.0 SD was used as the definition of macrosomia. When the >90th percentile (> +1.28 SD) definition was used in the same pregnancies, 37.1% of the newborn infants were macrosomic.

In the present work (Study II) the fasting plasma glucose value of the 2-hour OGTT correlated well with fetal macrosomia, which is in agreement with the results of other studies (Lindsay et al. 1989, Sermer et al. 1995, Fadl et al. 2006, Metzger et al. HAPO 2008). In contrast, the 2-hour value of the OGTT in the present study did not correlate with fetal macrosomia, which differs from the finding in the HAPO study (Metzger et al. HAPO 2008). The explanation for this difference could be that the number of subjects in the present study was too small, or that the difference could be due to ethnic (genetic) differences in the populations studied.

In our series the 2-hour value of the OGTT alone, as proposed by the WHO (Alberti and Zimmet 1998), could not be used to separate GDM pregnancies with an increased risk of fetal macrosomia from those with a low risk. Fetal

macrosomia occurred as frequently in GDM women with a 2-hour glucose value below 7.8 mmol/l as in GDM women with a 2-hour value above 9.0 mmol/l (Study II).

It has been reported that insulin treatment in addition to diet results in lower rates of macrosomia compared with diet treatment alone in GDM pregnancies (Coustan and Imarah 1984, Langer et al. 2005b). In a randomized study, women with GDM, with diet and insulin treatment as needed, had lower rates of macrosomia and other perinatal complications compared with women with GDM having routine care without GDM treatment (Crowther et al. 2005). It is therefore important to achieve normoglycemia by means of adequate treatment in all GDM pregnancies.

The high frequency of macrosomic fetuses in insulin-treated GDM pregnancies in the present study suggests that the treatment of GDM was insufficient or it was started too late. It is also possible that what was considered good glycemic control was not good enough to prevent fetal macrosomia. One of the main aims of future research is to develop methods that would identify in early pregnancy, or even before pregnancy, those women who will develop GDM, especially those with an increased risk of having a macrosomic fetus.

1.4 Neonatal brachial plexus injury

The incidence of shoulder dystocia and Erb's palsy are increased among the newborn infants of GDM pregnancies (Gilbert et al. 1999, Mollberg et al. 2005), and also among LGA infants of non-diabetic pregnancies (Ecker et al. 1997, Kolderup et al. 1997, Bryant et al. 1998). Shoulder dystocia was not recorded in the present work (Studies I and II) because of the difficulty of defining it. In the present study Erb's palsy occurred in vaginal deliveries at the same high frequency in both diet- and insulin-treated GDM pregnancies (Study II). Although the absolute birth-weights in the diet-treated GDM and control pregnancies

differed only slightly, Erb's palsy occurred more than five times more often in the diet-treated GDM group than in the controls. The most likely explanation for this difference is the unfavorable effect of GDM on fetal body composition (Neggers et al. 1995, Catalano et al. 2003). Newborn infants of mothers with GDM have large shoulder/head and chest/head ratios compared with the newborn infants of healthy women (Modanlou et al. 1982, Ballard et al. 1993). It is noteworthy that 13 of the 15 newborn infants with Erb's palsy among the GDM pregnancies in the present work (Study II) weighed more than 4000 g at birth.

It is difficult to identify pregnancies at an increased risk of shoulder dystocia and brachial plexus injury. Fetal shoulder width cannot be reliably assessed by ultrasongraphy, in contrast to fetal abdominal circumference measurement (Landon et al. 1989). However, fetal weight, shoulder width and maternal pelvic capacity can be measured by magnetic resonance imaging (MRI) (Baker et al. 1994, Spörri et al. 1997, Tukeva et al. 2001). Therefore, MRI should be used more frequently for fetal shoulder width and body volume (weight) measurements, especially in diabetic pregnancies and when fetal macrosomia is suspected. It is important that every obstetrical unit has guidelines how to manage shoulder dystocia in order to prevent brachial plexus injury.

In the present study insulin-treated GDM patients had a significantly higher cesarean section rate than the diet-treated GDM patients (Study II). This may be one of the reasons why Erb's palsy was not more frequent in the insulin-treated GDM pregnancies than in the diet-treated pregnancies, although fetal macrosomia occurred four times more frequently in the insulin-treated pregnancies than in the diet-treated GDM pregnancies. It is also possible that the diagnosis of diet-treated GDM could have given a false sense of safe vaginal delivery compared with the insulin-treated GDM women, although the diagnosis of GDM seems to favor the decision to deliver by cesarean section (Sermer et al. 1995, 1998).

2. Type 1 diabetes mellitus

2.1 Glycemic control during pregnancy

In the present study, glycemic control in Type 1 diabetic pregnancies was mainly based on home monitoring of plasma glucose values and repeated HbA_{1c} measurements in the outpatient maternity clinic, which is in line with international recommendations (Gabbe and Graves 2003, Jovanovic and Kitzmiller 2008).

2.2 Fetal malformations

The majority of clinical studies on Type 1 diabetic pregnancies indicate that poor glycemic control immediately before conception or during the first trimester is associated with an increased risk of fetal malformations (Miller et al. 1981, Fuhrmann et al. 1983, Ylinen et al. 1984, Rose et al. 1988, Greene et al. 1989, Steel et al. 1990, McElvy et al. 2000, Evers et al. 2004, Inkster et al. 2006, Nielsen et al. 2006). These results support the concept that maternal hyperglycemia is responsible for the increased risk of fetal malformations. It was previously thought that fetal malformations occur only when the maternal mean glucose level is above a certain threshold level (Greene et al. 1989, Hanson et al. 1990). However, the results of the present work (Study III) suggest that an increased risk of fetal malformations occurs even when HbA_{1c} levels are only slightly increased in early pregnancy. In fact, only women with normal HbA_{1c} levels in early pregnancy showed the same low fetal malformation rate as the non-diabetic control women. This is the first study in which the results suggest that there is no increased glucose threshold above which an increased risk of fetal malformations occurs.

The exact pathogenic mechanism by which hyperglycemia causes fetal malformations in diabetic pregnancies is not known. Most likely several mechanisms exist. Experimental studies suggest that oxidative stress may have an important role in the teratogenicity of diabetic pregnancies (Cederberg and Eriksson 2005). The observation that the central nervous system malformations in our series were associated with relatively low HbA_{1c} values suggests that factors other than maternal hyperglycemia could also be involved in the pathogenesis of some fetal malformations in diabetic pregnancies. Folic acid supplementation is included in the recommendations for the care of Type 1 diabetic pregnancies (Ray et al. 2001).

At our hospital, the rate of major malformations in the newborn infants of women with Type 1 diabetes decreased from 7.7% in 1978–1982 (Ylinen et al. 1984) to 4.4% in 1988–1997 (Study III). During the same time period, the mean level of HbA_{1c} of the first measurement in early pregnancy decreased from 8.2% to 7.7%, which at least partly explains the reduction in the rate of fetal malformations. The most likely cause for the improved glycemic control was the introduction of home monitoring of glucose levels in the 1980s. Pre-pregnancy counceling and centralization of the care of Type 1 diabetic pregnancies may also have resulted in the improved glycemic control.

2.3 Preeclampsia and pregnancy-induced hypertension

2.3.1 Risk factors

The increased risk of preeclampsia in Type 1 diabetic pregnancies (White 1949, Pedersen et al. 1974, Hanson and Persson 1998, Sibai et al. 2000) was also observed in the present work (Study IV). The most important risk factor of preeclampsia in women with Type 1 diabetes is nephropathy (White 1949, Pedersen 1977). On the other hand, it is difficult to define superimposed preeclampsia in women with diabetic nephropathy (Hanson and Persson 1998).

In addition to the duration of diabetes and nulliparity, we found that diabetic retinopathy and poor glycemic control were significant independent risk factors of preeclampsia. The observations are in accordance with those in previous reports (Funai et al. 2005, Howarth et al. 2007, Luo et al. 2007). Furthermore, it has been reported that the frequency of preeclampsia increases with increasing severity of diabetic complications (Sibai et al. 2000). However, in a recent study no relationship between the risk of preeclampsia and the duration of diabetes was observed (Howarth et al. 2007).

In the present work the risk of PIH among women with Type 1 diabetes without nephropathy was twice that of non-diabetic controls (Study IV). Garner et al. (1990) and Siddiqi et al. (1991) have also reported an increased risk of PIH in women with Type 1 diabetes. Unlike preeclampsia, PIH was not associated with poor glycemic control during pregnancy in the present study, which was also an observation noted in a Swedish study (Hanson and Persson 1998). In a follow-up study carried out by Gordin et al. (2007) it was suggested that preeclampsia, but not PIH, increased the risk of diabetic nephropathy later in life. These observations suggest that preeclampsia and PIH are two different entities with different pathogenetic mechanisms, at least in pregnancies complicated by Type 1 diabetes.

2.3.2 Glycemic control

The association between poor glycemic control in early pregnancy and the occurrence of preeclampsia in women with Type 1 diabetes observed in Study IV has been reported previously (Combs et al. 1993, Rosenn et al. 1993, Hsu et al. 1996, 1998, Hanson and Persson 1998). The results of the present study indicate that glycemic control during the first half of pregnancy influences the occurrence of preeclampsia in the second half of pregnancy. Each 1% unit increment in the level of HbA_{1c} during the first trimester of pregnancy corresponded to a 1.6-fold increase in the risk of preeclampsia.

It has been suggested that improvement of glycemic control during pregnancy reduces the risk of preeclampsia (Hsu et al. 1996). The results of the present study are in accordance with this. After adjusting for confounding factors, each 1% unit decrement in the HbA_{1c} level achieved by mid-pregnancy reduced the risk of preeclampsia by a factor of 0.6. However, a change in HbA_{1c} values during the latter half of pregnancy did not influence the occurrence of preeclampsia. This is a further example of the importance of maintaining and improving glycemic control throughout pregnancy in order to decrease both maternal and perinatal complications in diabetic pregnancies.

The mechanism is not clear, why good glycemic control in early pregnancy exerts a beneficial effect during the latter half of pregnancy on the incidence of preeclampsia. One could speculate that a possible reason could be the so called 'metabolic memory' phenomenon, which was observed in studies examinating the long term effects of good glycemic control on diabetic complications (DCCT 2000, Genuth et al. 2005).

CONCLUSIONS

1. Women with gestational diabetes mellitus have an increased risk of preeclampsia and/or pregnancy-induced hypertension compared with non-diabetic pregnant women.

2. The fasting plasma glucose value in the 2-hour OGTT is a better predictor of fetal macrosomia than the 2-hour value. A 24-hour glucose profile carried out within a week after the diagnosis of GDM distinguishes between pregnancies with a low risk (diet-treated) and a high risk (insulin-treated) of fetal macrosomia.

3. No threshold level of mean maternal plasma glucose concentrations exists, above which fetal malformations are likely to occur. Even a slightly increased HbA_{1c} level during early pregnancy in women with Type 1 diabetes mellitus carries an increased risk of fetal malformations.

4. In women with Type 1 diabetes, poor glycemic control during the first trimester of pregnancy is associated with an increased risk of preeclampsia but not pregnancy-induced hypertension. Improvement of glycemic control by mid-pregnancy reduces the risk of preeclampsia.

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